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ANTIBODY RESPONSE OF PATIENTS WITH PNEUMOCOCCIC PNEUMONIA TREATED WITH SULFADIAZINE AND SULFATHIAZOLE *

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THE results of immunological studies of a large number of patients with pneumococcic pneumonia treated with sulfapyridine were reported recently from this laboratory.[1] As far as could be determined, the antibody response of these patients was comparable in every respect to that resulting from spontaneous recovery of similar cases included in previous investigations in which the same methods were employed.[2-6] The tests used in the study of the serums from the sulfapyridine treated cases included: agglutinins, which were determined in every instance; mouse protection tests, which were carried out in all cases due to some of the common pneumococcus types; and pneumococcidal and opsonic tests, which were done only in a few cases.

Shortly after this paper was published, Kneeland and Mulliken [7] reported on the antibody formation in 19 cases of lobar pneumonia treated with sulfapyridine. Employing only the precipitin reaction with type-specific polysaccharide, they demonstrated an excess of antibody in only four of the 19 cases, and even in these four cases antibodies were not noted until after the patients' temperature had been normal for about a week. They concluded that sulfapyridine has supplanted, at least to some degree, the immune mechanism in cases treated with this drug. They also felt that when antibody formation did occur in such cases it proceeded at a slower rate

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than in untreated cases, probably because the stimulus to antibody formation was lessened through the action of the drug on the invading organism.

In a subsequent paper [8] the same authors, again employing only the precipitin test, demonstrated the appearance of an excess of type-specific antibody in 16 of 21 patients with lobar pneumonia treated with sulfathiazole. They interpreted their findings as indicating that there is a greater stimulus to antibody formation in patients treated with sulfathiazole than in those treated with sulfapyridine. This, in turn, led them to the conclusion that sulfapyridine was a more powerful antipneumococcal agent than sulfathiazole.

Because of the importance of these implications with respect to the general problem of the relation of modern chemotherapy to the immune response to infections, it was felt that, in view of the wide discrepancies in the results, further studies were necessary. In the present paper are presented the results of antibody studies in two groups of patients with pneumococcic pneumonia, one treated with sulfathiazole and the other treated with sulfadiazine. Sera from these patients taken at intervals during and after chemotherapy were tested for agglutinins and mouse protective antibodies against the homologous type pneumococci and for precipitins against the corresponding type-specific polysaccharide. This offered an opportunity to compare the results of the three tests in individual cases. These results, together with those previously reported, also permitted a comparison of the response of groups of patients treated with three different sulfonamide drugs.

Materials and Methods

The patients studied were all admitted to the Boston City Hospital during the 1940–1941 season and all had clinical and roentgen-ray evidence of pneumonia. For the most part, patients with Types I, II, V and VIII pneumococci were chosen, since these were the frequently occurring types which have been found in this laboratory to be most satisfactory for mouse protection tests with sera of patients with pneumonia. A few cases with other types were included, but protection tests were not carried out with their serums. A blood culture was made in every instance before drug therapy was started. Sputum typings were made both before and after mouse inoculations. Similar dosages were used in almost all cases, namely, an initial dose of 2 or 4 grams followed by 1 gram every four hours until treatment was stopped. In a number of the sulfadiazine treated cases, however, the dose was reduced to 1 gram every six hours after essential recovery had taken place.

Blood for the serological tests and for the chemical determination of the concentration of the drug was obtained at frequent intervals during and after therapy. The *mouse protection tests* were carried out by the simultaneous inoculation of 0.2 c.c. of serum and decimal dilutions of stock strains of pneumococci which have been kept at maximum virulence by frequent mouse passage. The titers are recorded as the maximum number of fatal

doses protected by 0.2 c.c. of serum. No attempt was made to determine "end points" by using serial dilutions of the patients' serums. Some of the serums were tested with as much as 10^7 lethal doses (0.01 c.c. of culture), but as a rule 0.001 c.c. or 10^6 lethal doses was the largest amount of culture used. The protection of mice against the latter dose of culture by 0.2 c.c. of serum may be considered as the equivalent of 5 units per c.c. of serum. *Agglutinations* were done by mixing serial dilutions of serum with an equal volume of formalinized saline suspension of a fully grown culture, incubating for two hours at 37° C. and reading after overnight ice box storage. The titer was read as the final dilution of serum which produced grossly floccular agglutination. For the *precipitin tests,* both the method recommended by Bullowa, Bukantz and de Gara [9] and that used by Kneeland and Mulliken [7] were employed for a large number of the serums. Since qualitatively similar results were obtained with both these methods, only the latter was used in subsequent tests. Stock 1 : 1000 solutions of the type-specific polysaccharides were used.* Preliminary titrations were made with serial saline dilutions of these antigens against serial dilutions of antipneumococcus rabbit serums of known potency. The latter dilutions were made in clear, normal human serum in order to approximate more nearly the conditions of the actual tests. The optimum dilution of the polysaccharides for detecting small amounts of antibody up to 100 units was found to be 1 : 50,000 and this dilution was therefore used routinely. In all instances final readings were made after an hour of incubation at 37° C. and overnight ice box storage. All heavy precipitates were recorded as ++, and definite positive tests with diluted serums were also classified as ++. All other definite positive tests with undiluted serum are recorded as + and those in which there was a very faint or doubtful precipitate were recorded as ±. The agglutination and precipitin tests were controlled with antigens of heterologous types, and saline controls were also included in the precipitin tests. Chemical determinations of the drug concentration were carried out by the method of Bratton and Marshall [10] with the aid of a Klett-Summerson colorimeter.

Results

The results of the antibody studies in 48 patients who were treated with sulfadiazine alone and recovered are shown in table 1. The results in 46 similar cases treated with sulfathiazole are given in table 2. The more relevant data concerning the pneumonia and the therapy are also included in each instance. When several successive serums obtained from the same patient showed identical results, only the first and the last of such serums are listed. None of the patients included in these two tables received antipneumococcus serum or vaccines and, because of the known antigenicity of the type-specific pneumococcus carbohydrates when given intracutaneously,[2, 11] skin tests with specific polysaccharides were not done at any time.

* Furnished by the Lederle Laboratories, Inc.

TABLE I

Patients Treated with Sulfadiazine

Number	Sex and age	Type	Sulfadiazine therapy		Day of crisis	Blood culture before treatment	Results of tests					
			Day begun	Amount (grams)			Day of disease	Blood sulfadiazine (mg./100 ml.)		Mouse protection	Agglutinins	Precipitins
								Free	Total			
1	M 46	I	4	48	5	0	4	—	—	0	0	0
							6	6.7	10.7	10^5	0	0
							10	6.6	8.0	10^6	4	++
2	M 35	I	2	63	3	+	3	6.5	7.9	0	0	0
							7	8.7	9.8	10^5	2	0
							11	—	—	10^5	2	0
							14	—	—	10^5	0	0
3	F 18	I	3	32	4	+	9	—	—	10^5	0	0
4	F 52	I	3	90	7	0	4	3.5	4.5	0	0	0
							7	12.8	12.8	10	0	0
							10	—	—	0	0	0
							13	—	—	10^5	4	+
							49	—	—	10^5	2	+
5	M 56	I	5	30	6	+	6	7.9	8.7	10^4	0	0
							8	—	—	10^5	0	0
							11	—	—	10^6	4	+
6	M 33	I	4	26	6	0	6	8.3	9.2	0	0	0
							8	8.0	8.0	0	0	0
							10	—	—	0	0	0
7	M 38	I	3	30	4	+	3	—	—	0	0	0
							4	9.5	12.4	0	0	0
							6	13.7	16.6	10^3	0	0
							8	—	—	—	0	±
							11	—	—	10^3	0	+
8	M 40	I	3	48	5	+	5	—	—	0	0	0
							7	5.7	5.7	10^3	0	0
							9	—	—	10^5	2	+
							18	—	—	10^4	2	0
9	M 31	I	5	26	6	0	7	—	—	10^5	2	0
							10	—	—	10^6	8	++
10	M 76	I	3	27	4	0	5	8.0	9.7	10	0	0
							9	—	—	10	0	0
							14	—	—	10^4	0	0
11	F 52	I	4	50	5	0	4	0	0	0	0	0
							6	—	—	10	0	0
							8	—	—	10^4	0	0
							10	—	—	10^5	0	+
							12	—	—	10^6	0	+
							14	—	—	10^5	2	+
12	M 23	I	3	39	4	0	4	8.0	9.3	10^5	0	0
							7	6.0	7.5	10^6	16	++
							19	—	—	—	4	++
13	M 39	I	3	30	4	+	3	—	—	0	0	0
							6	5.3	5.3	10^4	0	+
							8	—	—	10^3	2	+
							12	—	—	10^3	2	+

For explanation, see *Materials and Methods*. — = test not done.

TABLE I (*Continued*)

Number	Sex and age	Type	Sulfadiazine therapy		Day of crisis	Blood culture before treatment	Results of tests					
			Day begun	Amount (grams)			Day of disease	Blood sulfadiazine (mg./100 ml.) Free	Blood sulfadiazine (mg./100 ml.) Total	Mouse protection	Agglutinins	Precipitins
14	M 38	I	2	30	3	0	5	8.5	9.9	10^2	0	0
							7	7.9	9.0	10^3	0	0
							9	7.7	8.8	10^5	0	0
							11	0	0	10^4	0	0
15	F 37	I	4	46	6	0	5	3.5	3.5	0	0	0
							7	5.6	6.6	0	0	0
							9	4.7	6.3	10^2	0	0
							11	3.2	3.8	10^5	4	++
							14	—	—	10^6	8	++
16	M 38	I	2	75	3	0	9	5.8	6.4	10^3	2	+
17	M 50	I	1	35	3	+	3	15.9	20.5	0	0	0
							5	12.6	15.4	10	0	0
							9	—	—	10^5	0	0
							11	—	—	10^6	0	0
18	F 43	II	2	30	4	0	5	6.4	7.8	10^5	2	0
							8	—	—	10^5	2	++
19	M 40	II	2	59	2	+	2	—	—	0	0	0
							3	7.4	8.7	0	0	—
							6	6.4	7.6	10^5	0	0
							9	5.2	6.3	10^4	4	0
							14	—	—	10^4	4	0
20	M 23	II	2	34	4	0	4	7.2	7.8	10^4	0	0
							6	9.8	11.5	10^6	16	++
							8	—	—	10^7	64	++
21	F 49	II	2	36	5	0	2	—	—	0	0	0
							5	5.2	5.2	0	0	0
							7	—	—	10^2	0	0
							9	—	—	10^6	8	++
							14	—	—	10^6	8	++
22	F 42	II	2	57	4	0	3	9.4	9.4	0	0	0
							6	7.6	8.2	10^5	2	0
							13	—	—	10^6	4	++
23	M 48	II	6	27	7	0	7	—	—	10^4	2	+
							10	10.8	12.6	10^6	8	+
							17	—	—	10^5	8	+
24	M 47	II	4	40	6	0	5	4.9	5.4	10^2	0	0
							7	8.7	9.3	10^6	16	±
							9	6.2	6.2	—	128	+
							11	3.7	4.3	10^7	256	++
							17	—	—	10^5	64	+
25	F 44	II	2	40	3	0	3	3.2	3.2	0	0	0
							5	6.9	7.5	10^3	2	0
							7	5.9	6.6	10^6	4	+
							9	—	—	10^6	8	++
							16	—	—	10^5	8	+

TABLE I (*Continued*)

Number	Sex and age	Type	Sulfadiazine therapy		Day of crisis	Blood culture before treatment	Results of tests					
			Day begun	Amount (grams)			Day of disease	Blood sulfadiazine (mg./100 ml.)		Mouse protection	Agglutinins	Precipitins
								Free	Total			
26	M 34	II	2	39	5	0	3	3.9	4.7	0	0	0
							5	12.6	16.0	10^5	2	0
							7	8.3	9.6	10^5	4	0
							9	—	—	10^6	8	+
27	M 53	II	4	30	6	0	5	6.7	7.7	0	0	0
							6	7.7	8.3	0	0	0
							9	—	—	10^3	2	+
							11	—	—	10^7	4	+
28	M 49	V	3	32	4	0	5	9.6	10.7	0	0	0
							8	5.7	6.3	0	0	0
							11	—	—	10	0	0
							14	—	—	0	0	0
29	M 44	V	5	30	6	0	5	0.8	1.1	0	0	0
							10	5.1	6.7	10^6	4	+
30	M 18	V	3	34	4	0	4	6.3	7.6	10^3	0	0
							5	8.5	9.6	10^6	0	0
							8	6.5	6.5	10^5	2	0
							11	—	—	10^5	2	+
31	M 16	V	4	54	6	0	5	4.5	5.4	0	0	0
							9	10.0	11.5	10^5	2	0
							11	8.9	10.8	10^6	8	0
							13	—	—	—	4	0
32	M 21	V	2	26	4	0	3	5.3	5.3	0	0	0
							5	9.8	11.9	10^4	0	0
							7	—	—	10^6	4	+
33	M 37	V	2	29	4	0	4	8.7	9.9	0	0	0
							6	7.7	8.4	10^3	0	0
							8	—	—	10^4	2	0
34	M 56	V	4	40	6	+	5	4.0	5.0	0	0	0
							7	8.5	9.4	10^5	0	0
							9	6.8	6.8	10^5	4	0
							13	—	—	—	16	++
							22	—	—	10^6	16	++
35	M 59	V	5	33	7	0	6	5.2	6.7	0	0	0
							8	7.2	8.5	0	0	0
							10	7.9	8.7	10^5	2	0
							14	—	—	10^6	4	0
36	M 64	V	2	32	3	0	2	—	—	0	0	0
							4	7.6	10.0	0	0	0
							8	—	—	10^6	4	++
37	M 19	V	4	30	6	0	5	1.8	1.8	0	0	0
							7	6.0	6.0	10^5	2	+
							9	—	—	10^7	16	++
							13	—	—	10^7	64	++

TABLE I (*Continued*)

Number	Sex and age	Type	Sulfadiazine therapy		Day of crisis	Blood culture before treatment	Results of tests					
			Day begun	Amount (grams)			Day of disease	Blood sulfadiazine (mg./100 ml.)		Mouse protection	Agglutinins	Precipitins
								Free	Total			
38	M 45	VIII	4	30	5	+	6	10.8	12.8	0	0	0
							9	7.2	7.2	10	0	0
							14	—	—	10^3	8	0
39	M 38	VIII	1	24	2	0	4	10.1	11.1	0	0	0
							7	—	—	10	0	0
							9	—	—	10^4	4	0
40	M 29	VIII	1	25	2	0	2	4.2	5.2	10	0	0
							4	8.4	10.8	10	0	0
							6	—	—	10^5	2	0
							8	—	—	10^6	4	0
41	M 62	VIII	3	40	4	0	4	8.4	10.4	10	0	0
							6	—	—	0	0	0
							9	—	—	10^5	4	0
							11	—	—	10^6	16	+
42	M 42	VIII	4	34	7	+	6	5.6	6.1	0	0	0
							7	7.7	8.7	10^2	2	0
							9	4.3	4.3	10^6	32	+
							11	5.9	5.9	10^5	64	++
							15	—	—	10^6	32	+
43	M 42	VIII	3	71	10	0	4	4.7	5.4	0	0	0
							9	6.7	7.6	0	0	0
							11	5.9	7.4	10^3	2	0
							13	5.5	6.4	10^2	4	0
							18	—	—	10^3	2	0
44	F 72	III	4	28	6	0	5	1.6	1.6	—	0	0
							6	9.1	12.8	—	0	0
							13	—	—	—	16	+
45	M 58	IV	4	60	9	0	4	—	—	—	0	0
							6	11.7	13.1	—	0	0
							8	6.7	6.7	—	0	0
							10	—	—	—	0	0
							12	7.3	8.1	—	0	0
							14	—	—	—	0	0
46	M 33	IV	3	38	6	0	3	5.1	5.1	—	0	0
							5	6.0	7.8	—	0	0
							8	7.3	8.4	—	16	++
							14	—	—	—	16	++
47	M 40	IV	4	32	7	0	5	4.8	4.9	—	0	0
							6	11.6	13.7	—	0	0
							8	7.2	8.2	—	0	0
							10	—	—	—	0	0
48	M 56	XVIII	2	37	6	+	2	—	—	—	0	0
							3	4.9	5.7	—	0	0
							6	3.6	3.6	—	0	0
							8	—	—	—	0	0
							11	—	—	—	4	0
							14	—	—	—	2	0
							18	—	—	—	0	0

TABLE II

Patients Treated with Sulfathiazole

Number	Sex and age	Type	Sulfathiazole therapy		Day of crisis	Blood culture before treatment	Results of tests					
			Day begun	Amount (grams)			Day of disease	Blood sulfathiazole (mg./100 ml.) Free	Blood sulfathiazole (mg./100 ml.) Total	Mouse protection	Agglutinins	Precipitins
1	F 14	I	2	30	3	0	2	—	—	10^2	0	0
							4	4.7	6.5	10^2	—	—
							6	—	—	10^5	2	0
2	M 47	I	7	25	8	+	13	—	—	10^5	32	++
3	F 63	I	5	15	6	0	8	—	—	10^6	4	++
							14	—	—	10^6	16	++
							19	—	—	—	16	++
4	F 30	I	5	30	7	0	6	—	—	10^5	0	0
							8	6.0	6.6	10^6	8	++
							11	—	—	—	16	++
5	F 34	I	4	32	5	0	6	9.1	10.9	10^5	2	+
6	M 33	I	6	39	7	0	6	—	—	10^6	8	++
							8	2.0	2.0	10^6	16	++
							10	2.6	2.6	—	16	++
7	M 76	I	4	26	6	+	6	—	—	10	0	0
							7	10.0	14.6	10	0	0
							9	—	—	10^3	0	0
							12	—	—	10^3	2	0
							15	—	—	10^5	4	+
8	M 57	I	5	25	8	0	6	—	—	0	0	0
							8	—	—	0	0	0
							10	—	—	10^3	0	0
							14	—	—	10	0	0
							20	—	—	0	0	0
9	F 35	I	5	23	7	0	6	4.4	5.5	10^4	0	0
							9	—	—	10^6	8	++
							13	—	—	—	4	++
10	M 43	I	5	29	8	0	6	4.4	5.7	10^2	0	0
							8	4.3	5.7	10^4	0	0
							10	—	—	10^6	4	++
							16	—	—	—	4	++
11	F 24	I	1	31	3	0	2	4.0	4.6	0	0	0
							3	5.8	7.0	0	0	0
							5	4.8	5.8	10^5	0	0
							7	—	—	10^5	8	+
12	F 24	I	4	63	6	0	5	—	—	0	0	0
							6	5.1	6.1	0	0	0
							8	4.3	5.2	10^5	0	0
							10	3.7	4.7	10^5	2	+
							16	4.3	5.6	10^5	4	+
							18	—	—	10^5	2	+
13	M 50	I	6	52	8	0	7	2.6	2.6	0	0	0
							8	3.9	4.9	10^3	0	0
							10	4.0	4.9	10^6	4	++
							12	3.8	4.4	10^6	8	++
							18	—	—	10^6	4	++

TABLE II (*Continued*)

Number	Sex and age	Type	Sulfathiazole therapy		Day of crisis	Blood culture before treatment	Results of tests					
			Day begun	Amount (grams)			Day of disease	Blood sulfathiazole (mg./100 ml.) Free	Blood sulfathiazole (mg./100 ml.) Total	Mouse protection	Agglutinins	Precipitins
14	F 48	I	3	33	4	0	3	—	—	0	0	0
							4	6.1	8.1	10^4	0	0
							6	—	—	10^5	4	+
							8	—	—	10^6	16	+
							10	—	—	10^6	16	++
							12	—	—	10^6	16	+
							20	—	—	0	0	0
15	M 60	I	2	111	A	+	5	2.5	3.3	10^3	0	0
							11	0	0	10^6	16	++
							16	1.0	1.0	10^5	8	++
16	M 40	I	3	50	5	+	4	6.0	7.7	0	0	0
							7	—	—	0	0	0
							10	2.5	3.1	10^7	32	++
							14	—	—	10^7	128	++
17	M 50	I	3	53	E	+	4	3.9	3.9	0	0	0
							5	4.5	5.2	0	0	0
							7	2.3	2.3	10^5	4	+
							11	2.1	2.1	10^6	32	+
							14	—	—	—	16	++
18	M 43	I	3	23	4	0	4	3.4	3.4	0	0	0
							6	—	—	10^3	0	0
							8	—	—	10^4	4	++
19	F 35	I	2	42	5	+	5	—	—	0	0	0
							7	4.0	4.8	0	0	0
							10	—	—	10^2	0	0
							12	—	—	10^2	0	0
							16	—	—	0	0	0
20	M 48	I	4	24	5	0	6	—	—	10^3	0	0
							8	3.2	4.7	10^4	0	0
							10	—	—	10^5	8	++
21	M 39	II	3	41	4	0	3	—	—	0	0	0
							6	4.1	5.5	10^6	8	++
							8	—	—	10^7	32	++
							11	0	0	10^7	64	++
							17	—	—	10^6	32	+
22	M 28	II	4	33	5	0	5	6.5	7.9	0	0	0
							6	5.3	6.6	10^3	0	0
							7	—	—	10^5	2	+
							9	—	—	10^5	2	++
							13	—	—	10^6	8	+
23	M 32	II	2	30	4	0	2	—	—	10	0	0
							3	3.5	3.5	0	0	0
							5	—	—	0	0	0
24	M 37	II	5	43	7	+	7	3.9	4.6	10^3	2	0
							9	1.8	1.8	10^7	32	++
							11	—	—	10^7	64	++
							17	—	—	10^7	32	++

TABLE II (*Continued*)

Number	Sex and age	Type	Sulfathiazole therapy		Day of crisis	Blood culture before treatment	Results of tests					
			Day begun	Amount (grams)			Day of disease	Blood sulfathiazole (mg./100 ml.)		Mouse protection	Agglutinins	Precipitins
								Free	Total			
25	M 34	II	2	43	12	+	3	5.4	6.1	0	0	0
							5	5.0	6.2	0	0	0
							6	3.5	4.1	10^5	0	0
							8	—	—	—	4	++
							14	—	—	10^7	32	++
26	M 50	II	3	40	5	0	3	—	—	0	0	0
							5	4.0	5.1	0	0	0
							7	3.3	3.3	10^5	2	0
							9	—	—	10^4	8	+
27	M 67	II	3	25	5	0	3	—	—	0	0	0
							5	10.7	15.3	0	0	0
							7	4.7	7.0	0	0	0
							9	—	—	0	0	0
							12	—	—	10^5	8	++
28	F 27	V	3	26	4	0	5	3.7	4.4	0	0	0
							7	3.4	4.4	10^2	0	0
							30	—	—	10^5	2	0
29	F 25	V	4	32	6	+	9	—	—	10^5	2	0
30	M 18	V	2	23	4	+	3	1.3	1.3	0	0	0
							6	—	—	0	0	0
							9	—	—	10^5	2	+
31	M 20	V	6	22	7	0	8	3.8	4.5	0	0	0
							10	—	—	10^5	2	++
							15	—	—	10^6	32	++
32	M 40	V	2	20	3	0	3	3.3	4.7	0	0	0
							4	—	—	10	0	0
							6	—	—	10^5	2	++
							8	—	—	10^6	4	+
33	M 44	V	4	26	5	0	5	2.1	3.0	0	0	0
							6	2.3	3.3	10	0	0
							8	2.8	4.1	10^5	2	0
							10	—	—	10^6	4	0
34	M 74	V	4	31	6	+	7	3.6	5.0	10	2	0
							19	—	—	—	16	±
							13	—	—	10^7	64	++
							17	—	—	—	32	++
35	M 41	V	5	37	6	0	5	—	—	10^3	0	0
							8	4.5	6.5	10^6	16	++
							10	3.9	5.0	—	32	++
							12	—	—	10^6	64	++
36	M 61	VIII	4	43	5	+	6	5.4	8.0	0	0	0
							8	4.7	6.2	10^5	8	0
							9	4.4	6.2	—	16	++
							11	6.1	8.4	10^6	64	++

TABLE II (*Continued*)

Number	Sex and age	Type	Sulfathiazole therapy		Day of crisis	Blood culture before treatment	Results of tests					
			Day begun	Amount (grams)			Day of disease	Blood sulfathiazole (mg./100 ml.) Free	Blood sulfathiazole (mg./100 ml.) Total	Mouse protection	Agglutinins	Precipitins
37	M 53	VIII	1	35	3	0	2	5.6	7.6	0	0	0
							6	—	—	10	0	0
							8	—	—	0	0	0
							10	—	—	0	0	0
							12	—	—	10	0	0
							20	—	—	0	0	0
38	M 17	VIII	3	24	4	0	5	3.6	4.5	0	0	0
							7	4.4	5.1	10	0	0
							9	—	—	10^5	8	±
							11	—	—	10^6	16	+
39	M 64	VIII	2	45	4	0	3	—	—	0	0	0
							4	7.2	8.8	0	0	0
							6	5.4	7.4	0	0	0
							8	5.3	6.4	10^4	4	0
							11	—	—	10^5	32	++
							13	—	—	10^6	64	++
40	M 39	III	7	128	E	0	9	1.9	1.9	—	2	0
							12	1.5	1.5	—	2	0
							14	—	—	—	2	0
							16	—	—	—	2	0
							18	—	—	—	2	0
							23	—	—	—	0	0
41	F 40	IV	2	35	3	0	3	—	—	—	0	0
							6	5.1	6.2	—	0	0
							8	7.4	9.4	—	2	0
42	F 23	IV	2	29	3	0	4	4.8	6.1	—	0	0
							6	—	—	—	2	0
							7	—	—	—	4	0
							9	—	—	—	4	±
43	M 71	IV	2	35	6	0	3	3.4	4.2	—	0	0
							5	5.3	6.5	—	0	0
							7	5.1	6.3	—	0	0
							9	—	—	—	0	0
							11	—	—	—	0	0
44	F 32	XIV	1	17	5	0	2	1.9	1.9	—	0	0
							5	0	0	—	0	0
							7	—	—	—	0	0
							9	—	—	—	4	0
							11	—	—	—	4	0
							13	—	—	—	4	0
45	M 60	XIV	2	28	3	0	4	2.6	3.5	—	0	0
							6	1.4	1.4	—	0	0
							8	—	—	—	0	0
46	F 42	XIV	4	42	7	0	5	4.6	5.2	—	0	0
							7	5.1	6.6	—	0	0
							9	2.9	3.7	—	4	0
							11	—	—	—	4	0
							13	—	—	—	8	0

For explanation, see *Materials and Methods*.
— = test not done.
A = arthritis (purulent).
E = empyema.

Almost all of the patients tested, both those treated with sulfadiazine and those who received sulfathiazole, developed mouse protective antibody at about the time of essential clinical recovery (listed in the tables as the day of crisis) or later. In occasional cases these antibodies were found as early as the fourth day of the disease, but in the great majority of the cases they were not demonstrated until the sixth day or later. The maximum titers varied considerably. In most cases the titers were found to increase gradually over the course of a few days, while in others the titers rose more rapidly.

Agglutinins appeared in the serum either at the same time as the mouse protective antibody or later. They were demonstrated on the fifth day in occasional cases, but usually appeared on the seventh day or later. In no instance were agglutinins demonstrated in the absence of protection, although the reverse was frequently found. When the protective titer rose gradually, the agglutinin titer usually followed. However, there was no strict quantitative correlation between the protective and agglutinin titers. In general, the results of the protection and agglutination tests were very similar to those previously obtained in patients treated with sulfapyridine.[1]

The precipitin test with the homologous type-specific polysaccharide was the least sensitive of the three tests used. In general, the results of this test stood in about the same relation to the agglutinins as the latter did to the protective titers. In none of the sulfathiazole treated cases were precipitins demonstrated in the absence of agglutinins or before the appearance of the latter, but this did occur in occasional sulfadiazine treated cases. In such instances, however, moderate titers of mouse protection were present at the same time.

Patients with Multiple Types of Pneumococci. Pneumococci of other types, in addition to those noted, were identified in the sputum of nine of the patients listed in tables 1 and 2. Among the sulfadiazine treated patients Type IV pneumococci were found in case 11, Type XX in case 17, Type VIII in case 18 and Type XV in case 35. Among the sulfathiazole treated patients, Type III pneumococci were identified in cases 19, 31 and 33, Type VIII in case 35 and Type XIX in case 40. The serums in these patients were tested for the presence of agglutinins for their respective type. In one of the patients (case 17, table 1), agglutinins for Type XX were found in a titer of 1 : 2 in each of the serums up to and including the ninth day, whereas in the next serum, obtained on the eleventh day, the titer was 1 : 8. In two sulfathiazole treated patients, Type III agglutinins were found in the first serum tested and the titers remained the same in later serums—in case 31 the titer was 1 : 4 and in case 33 the titer was 1 : 2. In the other six patients agglutinins were not demonstrated for the second pneumococcus type in any of the bloods obtained.

Cases Receiving Antipneumococcus Serum in Addition to Chemotherapy. In addition to the cases listed in tables 1 and 2, there were 14 patients with Type I, II, V or VIII pneumococcus pneumonia who received antipneu-

TABLE III

Maximum Titers of Antibodies in Recovered Cases of Pneumococcus Types I, II, V and VIII Pneumonia Treated with Sulfadiazine, Sulfathiazole and Sulfapyridine

Drug	Type	No. of Cases	Mouse protection				Agglutinins				Precipitins		
			0 or 10	10^2 or 10^3	10^4 or 10^5	10^6+	0	2 or 4	8 or 16	32+	0	+(±)	++
Sulfadiazine	I	17^7	1	2^1	8^5	6^1	6^3	8^4	3	0	6^3	7^4	4
	II	10^1	0	0	2^1	8	0	4^1	4	2	1^1	3	6
	V	10^1	1	0	2	7^1	1	6	2^1	1	4	3	3^1
	VIII	6^2	0	2^1	1	3^1	0	3	2^1	1^1	4^1	1	1^1
	Total	43^{11}	2	4^2	13^6	24^3	7^3	21^5	11^2	4^1	15^5	14^4	14^2
Sulfathiazole	I	20^6	0	2^1	6^2	12^3	2^1	6^1	9^1	3^3	3^1	4^1	13^1
	II	7^2	1	0	2	4^2	1	0	3	3^2	1	1	5^2
	V	8^3	0	0	3^2	5^1	0	5^2	3^1	0	3^1	1^1	4^1
	VIII	4^1	1	0	0	3^1	1	0	1	2^1	1	1	2^1
	Total	39^{12}	2	2^1	11^4	24^7	4^1	11^3	16^2	8^6	8^2	7^2	24^5
Sulfapyridine *	I	19^{11}	1	2^2	5^3	11^6	3^1	5^4	8^4	3^2			
	II	6^1	1	1	3	1^1	1	1	2	2^1			
	V	11	1	0	2	8	3	3	2	3			
	VIII	15^2	3^2†	6	5	1	3	7^2	3	2			
	Total	51^{12}	6^2	9^2	15^3	21^7	10^1	16^6	15^4	10^3	Not done		

Superscripts represent the numbers of patients who had positive blood cultures before treatment.
* Summarized from previous report by Finland, Spring and Lowell.[1]
† The 2 bacteremic patients each acquired mouse protective antibody against 10 LD.

mococcus serum after one to five days of chemotherapy and whose bloods were tested for antibodies. Eight of these patients were treated with sulfadiazine and six with sulfathiazole. Antibodies were demonstrated in only three of the 14 patients in the blood obtained before the first dose of serum was given. One patient treated with sulfadiazine developed agglutinins and protective antibodies but not precipitins, whereas in another treated with this drug and in one treated with sulfathiazole the antibodies were demonstrable by all three tests before antiserum was administered. In the remaining 11 patients no antibodies could be demonstrated at this time. In all the 14 patients, including three who died, high titers of agglutinins, precipitins and mouse protection for the homologous pneumococcus were found in all the bloods obtained after the antiserum was given.

Comparison of Antibody Response in Patients Treated with Three Different Sulfonamides. The maximum titers of antibodies obtained in all the recovered cases of sulfadiazine and sulfathiazole treated Types I, II, V and VIII pneumococcus pneumonia are summarized in table 3. In this table is also included a summary of the results of protection and agglutination tests in the corresponding sulfapyridine treated cases previously reported.[1] There was no significant difference in the results obtained in each of the three groups of cases. This is best seen by comparing the results of the mouse protection tests in the Type I cases. While some variations are noted among the other types, they are not great considering the limited numbers of cases and the large number of variables involved.

Discussion

The data presented indicate that, generally speaking, the antibody response of patients with pneumococcus pneumonia who recover following treatment with effective sulfonamide drugs is the same regardless of the drug used. Furthermore, a comparison of these results with the results of comparable studies in similar patients without chemotherapy or specific serotherapy indicates that the antibody response is not influenced by chemotherapy. This is in accord with the findings in experimental pneumococcal infections in mice treated with sulfapyridine from which McIntosh and Whitby[12] concluded that: "The administration of sulphonamide drugs has no stimulating action on the body defences, nor does such administration affect the quality, quantity, or speed of production of recognised specific antibodies." Levine, Larson and Bieter[13] likewise demonstrated the development of a high degree of specific immunity in rabbits experimentally injected with virulent pneumococci and treated with sulfapyridine. The latter authors began chemotherapy one hour after the infection was produced. They also demonstrated the development of a species-specific immunity which is explicable on the basis of their choice of the intracutaneous route for the infections.[14]

The conclusions of Kneeland and Mulliken [7, 8] with respect to the effect of chemotherapy on the antibody response to pneumococcic infections are not in agreement with the results of the present studies or with those previously reported.[1] Likewise, their conclusion that sulfapyridine is a somewhat more powerful antipneumococcal agent than sulfathiazole has not been borne out by the accumulated experimental and clinical data.

Summary and Conclusions

Antibody studies were carried out in two groups of patients with pneumococcic pneumonia, one treated with sulfadiazine and the other treated with sulfathiazole.

The antibody response in these two groups of patients was very similar, as judged by the results of the mouse protection, agglutinin and precipitin tests.

The results of mouse protection and agglutinin tests in these two groups of cases were essentially the same as those previously reported in sulfapyridine-treated cases and in patients who recover without specific serum or chemotherapy.

The precipitin test with type-specific polysaccharide is the least sensitive of the three tests employed in this study as a measure of antibody production in patients with pneumococcic pneumonia, the mouse protection test is the most sensitive and the agglutination test is intermediate.

REFERENCES

1. Finland, M., Spring, W. C., and Lowell, F. C.: Immunological studies on patients with pneumococcic pneumonia treated with sulfapyridine, Jr. Clin. Invest., 1940, xix, 179.
2. Finland, M., and Sutliff, W. D.: Specific cutaneous reactions and circulating antibodies in the course of pneumonia. I. Cases receiving no specific therapy, Jr. Exper. Med., 1931, liv, 637.
3. Finland, M., and Winkler, A. W.: Antibody response to infections with Type III and the related Type VIII pneumococcus, Jr. Clin. Invest., 1934, xiii, 79.
4. *Idem:* Antibody response to infections with Type II and the related Type V pneumococcus, *Ibid.*, p. 97.
5. Winkler, A. W., and Finland, M.: Antibody response to infections with the newly classified types of pneumococci (Cooper), *Ibid.*, p. 109.
6. Finland, M., Tilghman, R. C., Ruegsegger, J. M., and Dowling, H. F.: Clinical and immunological observations in cases of pneumococcus Type VII pneumonia treated with type-specific antibody, Am. Jr. Med. Sci., 1937, cxciii, 59.
7. Kneeland, Y., and Mulliken, B.: Antibody formation in cases of lobar pneumonia treated with sulfapyridine, Jr. Clin. Invest., 1940, xix, 307.
8. *Idem:* Antibody formation in cases of lobar pneumonia treated with sulfathiazole, *Ibid.*, p. 735.
9. Bullowa, J. G. M., Bukantz, S. C., and de Gara, P. F.: The balance between capsular polysaccharide and antibody in relation to prognosis and therapy in pneumococcal pneumonia, Ann. Int. Med., 1941, xiv, 1348.
10. Bratton, A. C., and Marshall, E. K., Jr.: A new coupling component for sulfanilamide determination, Jr. Biol. Chem., 1939, cxxviii, 537.

11. (*a*) FRANCIS, T., and TILLETT, W. S.: Cutaneous reactions in pneumonia. The development of antibodies following intradermal injection of type-specific polysaccharides, Jr. Exper. Med., 1930, lii, 573.
(*b*) FINLAND, M., and SUTLIFF, W. D.: Specific antibody response of human subjects to intracutaneous injection of pneumococcus products, *Ibid.*, 1932, lv, 853.
(*c*) FINLAND, M., and DOWLING, H. F.: Cutaneous reactions and antibody response to intracutaneous injections of pneumococcus polysaccharides, Jr. Immunol., 1935, xxix, 285.
(*d*) FINLAND, M., and BROWN, J. W.: Reactions of human subjects to the injection of purified type-specific pneumococcus polysaccharides, Jr. Clin. Invest., 1938, xvii, 479.
12. MCINTOSH, J., and WHITBY, L. E. H.: The mode of action of drugs of the sulphonamide group, Lancet, 1939, i, 431.
13. LEVINE, M., LARSON, W. P., and BIETER, R. N.: Active immunity to pneumococci in rabbits protected by sulfapyridine, Proc. Soc. Exper. Biol. and Med., 1939, xlii, 515.
14. JULIANELLE, L. A.: Reactions of rabbits to intracutaneous injections of pneumococci and their products. I. The antibody response, Jr. Exper. Med., 1930, li, 441. II. Resistance to infection. *Ibid.*, p. 449.

FURTHER STUDIES ON RECURRENCES IN PNEUMOCOCCIC PNEUMONIA WITH SPECIAL REFERENCE TO THE EFFECT OF SPECIFIC TREATMENT *

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In a previous paper Finland and Winkler [1] presented an analysis of 57 cases with recurrent attacks of pneumococcic pneumonia. Most of these cases occurred before the present classification of pneumococci [2] came into use. In a large proportion of the cases, the pneumococci were, therefore, classified as Group IV. Since that time, a much larger group of cases has been accumulated. Pneumococcus typing has improved in efficiency as a result of the introduction of the Neufeld method [3] and of the more complete classification of the types. Much new information also has been gained about the "higher" types of pneumococci, especially with respect to their rôle in carrier states and as incitants of disease. During this period, moreover, profound changes have occurred in the treatment of pneumonia. The use of specific antipneumococcic serums for types other than I and II and, in the past three years, the introduction and extensive employment of sulfonamide drugs have appreciably altered the course and outcome of attacks of pneumococcic pneumonia. The present study was undertaken in an attempt to determine whether any definite change has occurred in the incidence or character of the recurrences in pneumonia as a result of the improved bacteriologic methods, the extended knowledge of pneumococcus types and newer methods of treatment.

Selection of Cases

The patients were treated for all their attacks at the Boston City Hospital and, in all but a few instances, they were treated on the Medical Services to which are admitted only patients over 12 years of age. No patient included in the first report is considered here unless he subsequently had another attack of pneumococcic pneumonia. Each patient had two or more distinct attacks of pneumonia with characteristic physical and roentgenographic findings during each attack. One or more types of pneumococci were isolated and identified serologically during each attack. Each patient was discharged and well before the onset of the succeeding attack, this arbitrary criterion being used to distinguish "recurrence" from "relapse." Attacks of pneumonia

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in which pneumococci were not isolated were excluded. The usual methods were employed for the isolation and typing of pneumococci.

Analysis of Cases

The following features of the cases will be considered: Age, sex and color; the number, character, and location of the pulmonary lesions in the recurrent as compared with the initial attacks; the interval between attacks; the pneumococcus types; the occurrence of positive blood cultures; the mortality in the recurrences, and the influence of the various kinds of therapy on the duration of disease and the frequency of recurrences. A limited number of observations regarding antibodies is also included.

Age, sex and color. Of the 168 patients with recurrent attacks of pneumococcic pneumonia all but one (aged 4) were over 13 years of age, and 37 were 50 years of age or older at the time of the initial attack. Forty-eight, or 26.2 per cent, of the patients were females. All but 12 were white.

Number of recurrences. The 168 patients had 191 recurrent attacks of pneumococcic pneumonia. In each of four patients, there were four recurrences (five attacks); in 14 cases there were two recurrences (three attacks); and the remaining patients each had a single recurrent attack. In the various tabulations, each recurrence is correlated with the initial attack unless otherwise indicated.

Character of the pulmonary lesion. In the initial attack 128, or 76 per cent, of the patients had lobar pneumonia and 40, or 24 per cent, had an atypical pulmonary lesion. Of the 191 recurrent attacks, 132 or 69 per cent were lobar pneumonia. The character of the lesion in the first attack and in each of the succeeding attacks in the same patient are compared in table 1.

Table I

Comparison of Pulmonary Lesions in First Attacks and in Recurrences

First Attack	Recurrence	Number	Per Cent
Lobar	Lobar	113	59
Lobar	Atypical	34	18
Atypical	Lobar	19	10
Atypical	Atypical	25	13
Total recurrences		191	100

Nearly three-fifths of the patients had lobar pneumonia in both the initial and the recurrent attacks. In less than 30 per cent of all the attacks the character of the lesion was different in the first and in subsequent attacks in the same patient.

Location of the pulmonary lesions. In table 2 the lobes involved in the initial and the recurrent attacks are compared. Eleven recurrences (of the total of 191) were omitted for lack of pertinent data. The frequency with

TABLE II

Comparison of Lung Involvement During First and Recurrent Attacks of Pneumococcus Pneumonia

Lung Involved During First Attack		Lung Involved During Recurrence									Total First Attack	
		Right Lung				Left Lung				Bilateral		
		Lower	Upper and/or Middle	Entire	Total	Lower	Upper	Entire	Total		Number	Per Cent
Right:												
Lower		18	10	0	28	9	1	1	11	11	50	28
Upper and/or Middle		7	3	0	10	4	0	0	4	1	15	8
Entire		3	2	1	6	5	0	0	5	1	12	7
Total		28	15	1	44	18	1	1	20	13	77	43
Left:												
Lower		16	11	3	30	14	4	1	19	8	57	32
Upper		1	1	0	2	1	1	0	2	0	4	2
Entire		1	1	1	3	0	1	0	1	0	4	2
Total		18	13	4	35	15	6	1	22	8	65	37
Bilateral		11	3	2	16	6	0	0	6	13	35	20
Total Recurrences	No.	57	31	7	95	39	7	2	48	34	177	—
	%	32	18	4	54	22	4	1	27	19	—	100

which the various lobes were involved, both in the initial attack and in the recurrences, was not essentially different from what has been found in large series of unselected cases of pneumococcic pneumonia.[4] There was no tendency for the recurrence to involve the lobe affected in the first attack more than any other lobe. The incidence of bilateral involvement in the early and later attacks was nearly identical. The recurrences, therefore, tended to be neither more localized nor more extensive than the initial attacks.

Secondary pneumonias. Chronic pulmonary disease to which the attacks of pneumonia were thought to be secondary was present in 25, or 15 per cent of the patients. Eight patients had chronic bronchiectasis; 13 had chronic passive congestion of the lungs due to various types of heart disease; two had chronic pulmonary tuberculosis; one had a lung abscess; and another had Boeck's sarcoid involving the lungs. These 25 patients accounted for 32 recurrent attacks. Only three had more than two attacks. Two of the three subjects who each had five attacks of pneumonia had bronchiectasis.

Interval between attacks (table 3). The shortest interval between essential recovery from one attack and the onset of another was seven days; the longest was 18 years. Of the 12 recurrent attacks which occurred within two months of the preceding attack, eight were in subjects with bronchiec-

TABLE III

Interval Between Attacks of Pneumococcus Pneumonia

Interval	Number of Attacks	Number of Attacks with Same Type in Successive Attacks
Less than 2 months	12	6
2 to 6 months	27	11
6 to 12 months	27	4
1 to 3 years	59	10
3 to 5 years	36	5
5 to 10 years	20	1
10 or more years	10	0
Total	191	37 (19.4%)

tasis, and in four of these eight the same type of pneumococci was isolated in each of two successive attacks. Of the 27 recurrences after two to six months, 12 were in subjects with chronic pulmonary disease, but only two of these were recurrences with the same type of pneumococcus in successive attacks. Of the 153 attacks that recurred after six months, only 12 were in patients with chronic pulmonary disease. It is usually thought that patients with chronic pulmonary disease are more likely to have recurrences of pneumonia at shorter intervals than those with otherwise normal lungs.

Altogether, the same type of pneumococcus was isolated in two successive attacks in the same subject in 37 of the 191 recurrences, or 19 per cent. In the 39 instances in which successive attacks occurred within six months, the same type was obtained both times in 17, or 46 per cent, while in the successive attacks that were more than six months apart, the same type occurred in 20 of 152 cases, or 13 per cent. In other words, successive attacks were associated with the same pneumococcus type three and one-half times as often if they occurred less than six months apart than if they occurred more than six months apart. As the interval between attacks increased, the frequency with which the same pneumococcus type appeared in successive attacks decreased progressively. This was equally true for patients with and for those without underlying chronic pulmonary disease. This may imply that persistence of pneumococci either in the carrier state or in foci of infection, rather than exogenous reinfection, accounts for a large proportion of the early recurrences of pneumonia with the same type of pneumococcus. Although in the majority of convalescent patients the homologous pneumococci disappear in a few weeks,[5] it is known that they may persist for as long as 25 months after an attack of pneumonia.[6]

Pneumococcus types. The frequency with which various types of pneumococci were isolated during the first and subsequent attacks is listed in table 4. The types in each of 20 patients in whom multiple types of pneumococci were isolated during one or more attacks are excluded from this table and shown separately in table 5. These results may be compared with data on a large number of cases of pneumococcic pneumonia reported from

this hospital for the period from 1929 to 1936.[7] This comparison has the advantage that the cases in both series were drawn from the records of the same hospital, and, to a certain extent, in the same period of time. In that report, 79 per cent of 2229 cases of lobar pneumonia were associated with pneumococci of types I, II, III, V, VII and VIII, while 21 per cent were

TABLE IV

Comparison of Predominant Types of Pneumococcus Recovered During First Attack and During Recurrence

Type	First Attack		Recurrence		Number with Same Type in First Attack and Recurrence
	Number	Per Cent	Number	Per Cent	
I	31	18.7	18	10.8	4
II	19	11.4	16	9.6	3
III	26	15.7	20	12.0	9
V	7	4.2	6	3.6	0
VII	11	6.6	12	7.2	0
VIII	12	7.2	13	7.8	2
Types I, II, III, V, VII, VIII	106	63.9	85	51.2	18
IV	3	1.8	8	4.8	0
VI	8	4.8	5	3.0	0
IX	3	1.8	3	1.8	0
X	6	3.6	2	1.2	0
XI	6	3.6	2	1.2	0
XII	2	1.2	6	3.6	0
XIII	2	1.2	0	0	0
XIV	5	3.0	7	4.2	1
XV	2	1.2	3	1.8	0
XVI	1	0.6	2	1.2	0
XVII	1	0.6	5	3.0	0
XVIII	6	3.6	1	0.6	1
XIX	3	1.8	12	7.2	1
XX	2	1.2	11	6.6	0
XXI	1	0.6	3	1.8	0
XXII	1	0.6	0	0	0
XXIII	1	0.6	1	0.6	0
XXV	3	1.8	2	1.2	0
XXVII	0	0	1	0.6	0
XXVIII	0	0	2	1.2	0
XXIX	0	0	2	1.2	0
XXXI	1	0.6	2	1.2	0
XXXII	2	1.2	0	0	0
Unclassified	1	0.6	1	0.6	0
All "Higher types"	60	36.1	81	48.8	3
Total	166	100	166	100	21

associated with other types (IV, VI, IX–XXXII). In the present study, 64 per cent of the first attacks were associated with types I, II, III, V, VII and VIII while in the recurrences only 51 per cent of the cases had pneumococci of these six types. This might imply that the type distribution in the present series of cases was atypical in that there was in each instance a

larger proportion of "higher" types. However, as already noted, 24 per cent of the initial attacks were atypical or bronchopneumonias, and 31 per cent of the recurrent attacks were in that category. In the series referred to previously,[7] it was found that only 43.9 per cent of 619 cases of atypical pneumococcic pneumonia were associated with types I, II, III, V, VII and VIII. In the present cases there was a somewhat greater proportion of atypical pneumonias in the recurrences than in the initial attacks. When due allowance is made for this factor, the type distribution in both the initial

TABLE V

Multiple Types of Pneumococci Isolated During One or More Attacks of Pneumonia

Case Number	Pneumococci Isolated		Associated Disease
	First Attack	Recurrence	
4	BMC	(1) IX, XIX, BMC (2) XXIX, BMC (3) IX, XVI, BMC (4) IX, XVI, XXIX XXXIII, BMC	Bronchiectasis
22	III	IX, XXIX	Lung Abscess
28	VII, XIII	V	
31	VII, VIII	V, VIII	
39	III	III, X	
41	X	VII, XXVIII	
46	XVI	XI, XVI, XVII	C.P.C.
54	VIII (BC), XXIX (Emp.)	XXII	Emp. (first attack)
59	III	III, I (BC)	C.P.C.
60	XVIII	I, XVIII	
72	III, X	III	
78	I	(1) IV (2) VII (3) III, XI (4) III, V	
91	III	XIX, XXVII	
103	III, XI, XVII	III, VIII, XV	
108	XVI, XXXII	VII	
133	I	XXII, XXIX	
151	VIII	VIII, XX, XXIX	C.P.C.
171	VI, VIII	XV, XIX	
184	VII, XXIX	XII, XVII, XXIX	Bronchiectasis
187	I	X, XIII	

BMC = Friedländer bacillus, type A.
BC = blood culture.
Emp. = empyema.
C.P.C. = chronic passive congestion of lungs due to heart disease of various types.

and recurrent attacks was about what might be expected in a series of unselected cases including both lobar and atypical pneumonias.

The number of instances in which the same type of pneumococcus was isolated in both the initial and recurrent attacks in the same patient was too small for the percentage distribution of types to be of particular significance. Nevertheless, the proportion of Types I and II was about what would be expected on the basis of the usual frequency of occurrence of these types in

pneumonia. Type III, however, accounted for 14 of the 37 cases with the same type in both attacks. At least two explanations are suggested for this high incidence of recurrences with this type. Type III is known to be one of the most frequent types isolated from healthy carriers.[8] In addition, there is reason to expect reinfection with this type frequently, since nearly one-third of the cases of Type III lobar pneumonia at autopsy were found to have gross or microscopic abscess formation in the lungs.[9]

In some cases in the present series, pneumococci were associated with other organisms including Friedländer's bacillus, influenza bacilli, staphylococci and hemolytic streptococci. The relation of the pneumococci to the etiology of the pneumonia, in some of these cases, may be open to some doubt.

In table 5, the cases with multiple types of pneumococci in one or more attacks are listed. In case 4, an example of chronic Friedländer's bacillus infection of the lungs, the various types of pneumococci were probably of little etiological significance. It has been pointed out that other organisms, including pneumococci, tend to appear in the sputum of patients with chronic Friedländer's bacillus pneumonia.[10] In seven of these 20 cases, the existence of chronic pulmonary disease made it likely that some, if not most, of the multiple types of pneumococci found were carrier types. The frequency with which certain types appeared in this group of cases was notable. Type III was found 12 times; Type VII, five times; VIII, six times; XVI, four times; and XXIX, seven times. The frequent presence of these types in repeated attacks of pneumonia suggests strongly that they were carrier types.

In a few cases, both types isolated in a single attack of pneumonia appeared to be significant organisms. Thus, in case 54, Type VIII was isolated from the blood and Type XXIX from empyema fluid. In case 60, in the first attack Type XVIII was present in the sputum while in the recurrence Types I and XVIII were present in both sputum and empyema fluid.

Bacteremia. A record of one or more blood cultures taken during the initial attack was available in 135 cases. Eighteen of these were positive for pneumococci, a bacteremic rate of 13.3 per cent. In the 191 recurrences, the results of blood cultures were recorded in 179; 29 were positive for pneumococci, or 16.2 per cent. To make a valid comparison between the two groups, however, the fatal recurrences had to be excluded. The corrected bacteremic rate for recurrent attacks which ended in recovery was then 13.1 per cent. There was, therefore, no difference between the incidence of bacteremia in initial attacks and in non-fatal recurrences. Moreover, these rates are similar to the incidence of bacteremia reported in a series of 853 non-fatal cases of pneumonia in this hospital.[11]

Five patients had bacteremia in both the first and subsequent attacks. Only one patient had bacteremia of the same type (II) in successive attacks, and these occurred 12 months apart. The following types were involved in successive attacks in the other four patients: V and XIX, XI and XIV, II and VII, and VIII and III. One other patient had bacteremia with Type

XII in the second attack, and Type XI in the third attack, but a negative blood culture in the initial attack.

Mortality. There were 21 deaths in 191 recurrent attacks of pneumonia, a mortality of 11 per cent. This is considerably lower than the average during the period of this study in this hospital. In 112 of these recurrent attacks, specific therapy in the form of antipneumococcus serums, sulfonamide drugs (sulfapyridine, sulfathiazole and sulfadiazine), or a combination of serum and sulfonamides was used. The mortality in this specifically treated group was 11.6 per cent. In 79 attacks in which no specific treatment was given the mortality was 10.1 per cent. Although the proportion of subjects over 50 years of age and those with multiple lobe involvement was approximately the same in both treated and untreated groups, the former had a bacteremic rate of 21 per cent while in the untreated cases, the bacteremic rate was only 6 per cent. It is obvious that the subjects who were treated were, on the whole, more seriously ill on admission and would be expected to have a higher mortality rate. Some of the patients who received no specific therapy were already recovering from their attack at the time of admission to the hospital.

Eight of the 29 patients who had bacteremia during recurrent attacks died. Of these 29 patients, 23 were treated with specific therapy and four died; of the five untreated bacteremic patients, three died. Two-thirds of the 21 patients who died were over 50 years of age. Five patients died of complicating diseases independent of the pneumonia.

Duration of acute disease in non-fatal attacks. The duration of acute illness during initial and subsequent attacks was one indication of the relative severity of recurrent pneumonia. In making such a comparison the effect of treatment of each attack was considered since specific therapy might be expected to modify the duration of an attack. In table 6, 128 initial attacks

TABLE VI

Duration of Acute Illness (Non-fatal Attacks) in Relation to Therapy

Therapy of First Attack	Number of Cases	Recurrence							
		No Specific Therapy				Specific Therapy			
		Duration Same within 2 Days in Both Attacks	Recurrence 2 or More Days Longer	Recurrence 2 or More Days Shorter	Total	Duration Same within 2 Days in Both Attacks	Recurrence 2 or More Days Longer	Recurrence 2 or More Days Shorter	Total
No specific therapy	80	12 (38%)	4 (19%)	14 (44%)	32 (100%)	14 (29%)	6 (13%)	28 (58%)	48 (100%)
Specific therapy	48	6 (46%)	5 (39%)	2 (15%)	13 (100%)	21 (60%)	6 (17%)	8 (23%)	35 (100%)
Total	128	18	11	16	45	35	12	36	83

and the same number of non-fatal recurrences were compared. Twenty-one fatal attacks and 41 attacks in which either the onset or termination was indefinite were omitted. "Specific therapy" refers to treatment with anti-pneumococcus serum (horse or rabbit), sulfonamide drugs (sulfapyridine, sulfathiazole and sulfadiazine), or both. Of 48 patients who had no therapy in the first and specific therapy in the recurrence, nearly three-fifths had an attack of shorter duration in the recurrence than in the initial infection. This might be expected as the result of specific treatment. Among the patients who had the benefit of specific therapy during both attacks the duration of acute illness was the same in both initial and recurrent attacks in three-fifths of the cases. In the group who had no specific therapy in either attack more than 80 per cent of the recurrences were of the same duration or shorter than the initial attack. It would seem, therefore, that apart from the effect of specific treatment, the duration of acute illness in recurrences tends to be the same or shorter than in the first attack.

On the whole, the recurrent attacks were, therefore, less severe than the general run of pneumonias in this hospital as judged by the mortality, the incidence of bacteremia, and the duration of acute illness.

Frequency of recurrence as related to type of therapy. There is a suggestion in the recent literature that recurrences of pneumococcic pneumonia may be more frequent in patients treated with sulfonamide drugs in their first attacks than was the case with serum therapy. Hodes and his associates [12] treated 71 children with pneumococcic pneumonia with sulfapyridine and noted that four had a second attack within two weeks of the cessation of the therapy. In three of these the relapse was caused by the same organism as in the first attack. Davies,[13] in a series of 154 cases in infants and children treated with sulfapyridine, had three recurrences at intervals of from 10 days to four months. In each case the same type of pneumococcus was found in successive attacks. Carey [14] treated 387 infants and children with sulfapyridine or sulfathiazole alone, and 148 with the combination of specific serum and sulfonamides. None of the patients treated with combination therapy had recurrences within a year, but 11 of the patients treated originally with drug alone had a recurrence with the same type of pneumococcus from three to seven days after discharge from the hospital. Among adults, Dowling and Abernethy [15] reported that six patients of 339 treated with sulfapyridine had recurrences after an interval of from nine to 25 days. Four were treated with sulfonamides alone and two with both serum and drugs. No case had the same type of pneumococcus in the recurrence as in the first attack. Hamburger and Ruegsegger [16] reported a recurrence of Type I pneumonia two weeks after recovery from an initial attack of Type I pneumonia. Sulfapyridine was given both times. The patient had bacteremia in the first attack and empyema during the second.

These reports raise a number of questions in regard to the frequency and nature of recurrences of pneumococcic pneumonia in relation to chemo-

therapy: (1) Is the incidence of recurrences different in adults and children? (2) Is the incidence of recurrences different when the initial attack is treated with serum or sulfonamides, or without either of these remedies? (3) Is there a greater tendency for recurrences with the same type of pneumococcus when the first attack is treated with drugs? (4) Is the interval between recurrences shorter in drug-treated patients? The factor of antibody response in relation to therapy will be considered in a subsequent section.

We have attempted to analyze our data with these questions in mind. Since all but one of the patients in this report were adults, no data are available with regard to the frequency of recurrences in children. Greene [17] reported that 80 out of 561 children (18.2 per cent) had more than one attack of pneumonia. No bacteriological data were presented nor was specific therapy employed. In adults, it has been estimated that 15 to 20 per cent of patients with pneumonia have a history of a previous attack of the disease,[1, 18] but no series of cases with bacteriological data has been reported with an incidence as high as that. At present, it is impossible to say whether recurrences are more or less frequent in infants and children as compared with adults.

Since antipneumococcal serums have been employed extensively in this hospital for a number of years and sulfonamide therapy (exclusive of sulfanilamide) has been in use only two and a half years, the total number of recurrences in the two groups cannot be compared. We have, however, compared the frequency of recurrences *within two years* of an initial attack of pneumonia treated with specific serum, sulfonamide drugs, both serum and drugs, and no specific therapy.

In the past six years, in the Boston City Hospital, there were approximately 2000 untreated, non-fatal cases of pneumococcic pneumonia. During this period, 60 patients returned to the hospital with a second attack of pneumonia within two years of the first untreated attack. This is an incidence of 3.0 per cent. During the same period about 700 non-fatal cases of pneumonia were treated with specific antipneumococcal serum alone. Nineteen of these returned to the hospital with pneumonia within two years of the first attack—an incidence of 2.7 per cent. From October 1938 to June 1941 about 1200 non-fatal cases of pneumococcal pneumonia were treated with sulfapyridine, sulfathiazole or sulfadiazine alone. Of these, 18 or 1.5 per cent, treated with drug alone in the first attack, had a recurrence within two years. During the same period about 200 non-fatal cases were treated with both specific serum and sulfonamides, and six of these (3.0 per cent) had a recurrence of pneumonia within two years.

These figures are only approximate and by no means represent the actual incidence of recurrence of pneumonia within two years of the initial attack. All the patients who had recurrences did not necessarily return to this hospital. The estimates given lend no support to the idea that recurrences are more frequent with drug therapy than in untreated patients or in those

treated with specific serum. The incidence of recurrences in this series of adults is essentially similar to that reported in children by Davies, and Carey, and in adults by Dowling and Abernethy. Only Hodes reported a higher incidence (5.6 per cent) in children.

In the three series of cases in infants and children quoted above all but one of the drug-treated patients had the same pneumococcus type in the recurrence as in the initial attack. A summary of the data on this point in the present series of cases is given in table 7. Although the number of cases is small, there is a striking tendency for the drug-treated cases and the drug-plus-serum-treated cases to have the same type during initial and subsequent attacks. Further analysis of these cases, however, offers some explanation for these differences.

Of the 18 patients who had a recurrence within two years of a drug-treated first attack, seven had preëxisting chronic pulmonary disease, and four of these had recurrences with the same type. Only one of the 19

TABLE VII

Relation of Therapy in First Attack to the Pneumococcus Type Found in Recurrences Within 2 Years

Therapy in First Attack	Recurrences within 2 Years		
	Total Number	Number with Same Type	Number with Different Type
No specific therapy	60	10	50
Serum	19	3	16
Sulfonamide drugs	18	10	8
Serum plus sulfonamides	6	3	3
Total	103	26	77

serum-treated cases, and 10 of the 60 patients who had no specific therapy during the first attack had chronic pulmonary disease. It is to be expected that recurrent attacks of pneumonia are more frequent in patients with chronic pulmonary disease, and 39 per cent of the drug-treated group fell into that category.

Two of the 10 drug-treated patients who had a recurrence with the same type had bacteremia in the first attack; two of the three patients who were treated with drug plus serum in the first attack and had a recurrence with the same type had bacteremia in the first attack. On the other hand, none of the group treated with serum alone, or treated non-specifically, who had recurrences with the same type had bacteremia in the first attack. Thus, the drug-treated group and the group treated with both drugs and serum had, on the whole, more severe initial attacks. It has been shown that focal purulent complications are more frequent in bacteremic than in non-bacteremic cases.[11] The chance for the persistence of pneumococci in foci in the lungs or elsewhere is probably greater in such cases.

The average interval between attacks in the drug-treated group was six months, in the drug-plus-serum-treated group 11 months, in the serum-treated group 17 months, and in the group without specific therapy, 11 months. It was shown (table 3) that the incidence of recurrence with the same type was greatest when the interval between attacks was less than six months.

When all factors are considered it seems likely that the greater tendency for recurrences to occur with the same type in both attacks in patients treated with drug alone in the first attack is to be explained on the basis of: (1) a higher percentage of chronic pulmonary disease; (2) a higher incidence of bacteremia in the first attack; and (3) a shorter interval between attacks. The first two factors may be obviously chance occurrences in a small series of cases. However, the greater number of patients with chronic pulmonary disease among those treated with sulfonamide drugs may have resulted from the more frequent inclusion of such cases for treatment with drugs where previously they were not considered for specific treatment and, therefore, less often studied bacteriologically. The shorter interval between attacks in drug-treated cases would be of considerable significance if it should be substantiated by further observations on a larger number of cases.

Immunity reactions. Antibody studies were done in a limited number of the patients who had two or more attacks of pneumonia. Only those with the same type of pneumococcus in each of successive attacks will be considered here. These patients may be grouped, according to type of treatment and the antibody response, into several categories:

(1) There were three patients who had serum treatment in the first attack with the development of antibodies, a recurrence with the same type of pneumococcus and no antibodies demonstrable on admission to the hospital at the time of the second attack. One had Type II pneumococcus in both attacks, and two had Type III. The shortest interval between attacks was 12 months. One of these patients had three attacks of Type III pneumonia and received serum after the second attack. The patient with Type II pneumonia had bacteremia in both attacks which were 12 months apart.

(2) Two patients received sulfonamide therapy in the first attack with the development of antibodies after crisis, and subsequently had a recurrence with the same type of pneumococcus and no antibodies demonstrable at the time of the second admission to the hospital. Both of these patients had Type III pneumonia in both initial and second attacks. The interval between attacks was six months in one case and 16 months in the other. One case had bacteremia in the first attack; neither case had bacteremia in the recurrent attacks.

(3) Two patients had homologous type-specific antibodies after crisis in the first attack which were still demonstrable at the time of the second admission and before the crisis in a recurrent attack which was associated

with the same pneumococcus type. One patient had Type I pneumonia for which she was treated with both serum and sulfapyridine, and homologous antibodies were demonstrated after the serum therapy. Six months later she suffered a recurrence of Type I pneumonia. Antibodies for Type I pneumococci were demonstrated in her blood serum on admission to the hospital 24 hours after onset of the second attack. She was treated with sulfathiazole in the second attack with prompt response. The organism in this case was "sulfonamide-fast" and the case has been reported previously.[19] Another patient was treated for Type I pneumonia with sulfathiazole and sulfadiazine five months after recovery from an initial attack of Type I pneumonia treated with sulfathiazole. Antibody studies were not carried out during the first attack, but one day after the onset of the recurrence a high titer of antibodies for Type I was demonstrable. This patient had bacteremia during the first attack but not in the recurrence.

(4) Two patients failed to develop antibodies after recovery from the first attack and later had recurrences with the same type. One of these patients was treated with sulfadiazine during his first attack of Type I pneumonia. He responded rapidly to treatment, but developed no antibodies five days after crisis at which time he left the hospital. He returned four months later, again with Type I pneumonia, and again responded well to sulfadiazine therapy. No antibodies were demonstrable in the patient's serum at the time of the second admission, on the day of his crisis, nor during a period of three weeks after crisis. The other patient had both Types III and VIII in one attack of pneumonia during which no specific therapy was given. No antibodies for either III or VIII were demonstrable during convalescence from this attack. Four years later he had another attack of pneumonia with Type VIII pneumococcus.

(5) Four patients were treated with bivalent serum in the first attack and had recurrences with the second type which was not infecting the patient the first time, but for which antibodies were present in the antipneumococcal serum. The intervals between attacks varied from 21 months to eight years. One other patient had a recurrence with the same type (II) 21 months after receiving monovalent serum for Type II pneumonia. Antibody studies were not done in these five cases.

In summary, therefore, patients may have two or more attacks of pneumonia with the same type of pneumococcus, regardless of whether they are treated with serum, with sulfonamides or non-specifically during the first attack, and regardless of whether or not they develop antibodies for the homologous type after the first attack. Moreover, recurrences are noted despite the presence of homologous antibodies at the time of onset of the recurrence. Since all these combinations occur, it is impossible to correlate the immunity state with the likelihood of recurrence. Such correlation must await the accumulation of a larger body of data than is available at present.

Comment

In general, the conclusions reached in the earlier study of recurrences [1] have been confirmed in the present analysis of a considerably larger number of cases. As in the first study more than three-fourths of the cases had the same type of pulmonary lesion (lobar or atypical) in both the first and subsequent attacks. The conclusion that the various lobes are involved with the usual frequency in both attacks and that there is no correlation between the site of initial involvement and that of reinfection has been confirmed in the present study. In the present study bilateral involvement was no more frequent in recurrent attacks than it was in first attacks.

The inverse relation of the interval between attacks and the frequency of recurrence with the same type of pneumococcus in successive attacks is more evident in the present study with the larger number of cases. The frequency of occurrence of the various types of pneumococci in both initial and recurrent attacks was about what might be expected in a series of unselected cases of lobar and atypical pneumonia. The relatively frequent occurrence of Type III in successive attacks in the same patient may be explained by the known tendency of this organism to persist both in the healthy and in the convalescent carriers. As in the previous study, the bacteremic rate in the recurrent non-fatal cases was not greater than in the initial attacks nor was the mortality higher than would be expected in a series of unselected cases. In general, the initial attacks were of ordinary severity, as judged by bacteremia, multiple lobe involvement and age distribution, in comparison with non-fatal but otherwise unselected attacks of pneumonia. When the effect of treatment was taken into account, recurrent attacks were in the large majority of cases of the same duration or shorter than the initial attacks. A similar conclusion was drawn in the first study.

There is no evidence from this study that recurrences are more frequent among drug-treated patients than among those treated with serum or with no specific therapy. There was, however, a greater tendency for second attacks to recur at shorter intervals and for the same type to occur in both attacks than was observed in the cases treated with serum or with no specific therapy. This was only partially accounted for by certain chance factors such as a greater number of cases with chronic pulmonary disease and a higher bacteremic rate in this group of cases. The tendency for the disease to recur at shorter intervals and with the same type in drug-treated cases is suggested also from pediatric literature [12, 13, 14] and in the report of Dowling and Abernethy.[15] It is difficult at present to assess the significance of this finding. It was evident from the previous study that the shorter the interval between attacks the more likely is the recurrence to be due to the same type of pneumococcus as the original attack. This is true regardless of the type of therapy employed in the first attack and is independent of any underlying chronic pulmonary disease. It may be related to persistence of the original infecting organism in the convalescent carrier state.

The rôle of immunity in relation to the tendency to recurrence of pneumonia is at present obscure. Evidence accumulated in this laboratory indicates that the antibody response of patients treated with sulfapyridine, sulfathiazole or sulfadiazine is no different from that observed in untreated patients who respond by spontaneous crisis.[20, 21] Kneeland and Mulliken,[22, 23] on the contrary, interpreted their findings as indicating a poorer antibody response in sulfapyridine treated cases. From the present data it would appear that any given case may or may not have a recurrence with the same type of pneumococcus irrespective of whether he develops antibodies after the first attack. At the time of the recurrence humoral antibodies may or may not be demonstrable. There is, of course, no way to predict what immunity state will result following an attack of pneumonia or how long such immunity will persist.

Summary and Conclusions

A study of 168 patients with 191 recurrent attacks of pneumococcic pneumonia is presented. The initial and subsequent attacks did not differ significantly in the character or site of the pulmonary lesions, or in the distribution of the types of pneumococci involved. There was no increased tendency for recurrent attacks to be bilateral. Chronic pulmonary disease was a predisposing factor in only 15 per cent of the patients. In such patients, the attacks tended to recur at shorter intervals. The duration of the recurrent attacks was the same or shorter than the original infections. The frequency with which the same type was present in successive attacks was inversely proportional to the length of the interval between attacks. Type III was more frequently present in successive attacks than any other type. Successive attacks with the same type of pneumococcus were not more frequent in patients with chronic pulmonary disease than in other patients. Recurrences were not more frequent in patients treated with sulfonamide drugs in the first attack than in those treated with serum or in those treated non-specifically, but there was a tendency in the drug-treated cases for second attacks to occur with the same type and at shorter intervals. There is some indirect evidence that early recurrences with the same type of pneumococcus are associated with a persistence of the carrier state. There is no correlation between the antibody response and the tendency of pneumonia to recur.

References

1. Finland, M., and Winkler, A. W.: Recurrences in pneumococcus pneumonia, Am. Jr. Med. Sci., 1934, clxxxviii, 309.
2. Cooper, G., Rosenstein, C., Walter, A., and Peizer, L.: The further separation of types among the pneumococci hitherto included in group IV and the development of therapeutic antisera for these types, Jr. Exper. Med., 1932, lv, 531.
3. Sabin, A. B.: Immediate pneumococcus typing from sputum by the Neufeld reaction, Jr. Am. Med. Assoc., 1933, c, 1584.

4. Cecil, R. L., Baldwin, H. S., and Larsen, N. P.: Lobar pneumonia. A clinical and bacteriological study of two thousand typed cases, Arch. Int. Med., 1927, xl, 253.
5. Stillman, E. G.: A contribution to the epidemiology of lobar pneumonia, Jr. Exper. Med., 1916, xxiv, 651.
6. Cruickshank, R.: Pneumococcal infections. II. Lobar pneumonia in the community, Lancet, 1933, i, 621.
7. Finland, M.: The significance of specific pneumococcus types in disease, including types IV to XXXII (Cooper), Ann. Int. Med., 1937, x, 1531.
8. Finland, M., Brown, J. W., and Barnes, M. W.: Immune reactions of carriers and non-carriers of type-specific pneumococci, Am. Jr. Hyg., 1940, xxxii, 24.
9. Finland, M., and Sutliff, W. D.: Infections with pneumococcus type III and type VIII, Arch. Int. Med., 1934, liii, 481.
10. Solomon, S.: Chronic Friedländer infections of the lungs, Jr. Am. Med. Assoc., 1940, cxv, 1527.
11. Tilghman, R. C., and Finland, M.: Clinical significance of bacteremia in pneumococcic pneumonia, Arch. Int. Med., 1937, lix, 602.
12. Hodes, H. L., Stifler, W. C., Jr., Walker, E., McCarty, M., and Shirley, R. G.: The use of sulfapyridine in primary pneumococcic pneumonia and in pneumococcic pneumonia associated with measles, Jr. Pediat., 1939, xiv, 417.
13. Davies, J. A. V.: The treatment of pneumococcal pneumonia in infants and children with sulfapyridine, New England Jr. Med., 1939, ccxxi, 734.
14. Carey, B. W.: The treatment of pneumonia in infants and children, Jr. Pediat., 1941, xviii, 153.
15. Dowling, H. F., and Abernethy, T. J.: The causes of secondary fever in sulfapyridine-treated pneumonia, Ann. Int. Med., 1941, xiv, 1815.
16. Hamburger, M., Jr., and Ruegsegger, J. M.: Early recurrence of sulfapyridine-treated type I pneumococcal pneumonia, New England Jr. Med., 1939, ccxxi, 445.
17. Greene, D.: Recurrence of pneumonia in infancy and in early childhood, Am. Jr. Dis. Child., 1936, li, 284.
18. Warr, O. S., and Alperin, J.: Lobar pneumonia. A report of 2039 cases, Ann. Int. Med., 1933, vi, 1474.
19. Lowell, F. C., Strauss, E., and Finland, M.: Observations on the susceptibility of pneumococci to sulfapyridine, sulfathiazole, and sulfamethylthiazole, Ann. Int. Med., 1940, xiv, 1001.
20. Finland, M., Spring, W. C., Jr., and Lowell, F. C.: Immunological studies on patients with pneumococcic pneumonia treated with sulfapyridine, Jr. Clin. Invest., 1940, xix, 179.
21. Finland, M., Strauss, E., and Peterson, O. L.: Antibody response of patients with pneumococcic pneumonia treated with sulfadiazine and sulfathiazole, Ann. Int. Med., 1942, xvi, 1–16.
22. Kneeland, Y., and Mulliken, B.: Antibody formation in cases of lobar pneumonia treated with sulfapyridine, Jr. Clin. Invest., 1940, xix, 307.
23. *Idem:* Antibody formation in cases of lobar pneumonia treated with sulfathiazole, *Ibid.*, p. 735.

TREATMENT OF THE NEUROSES BY CLASS TECHNIC *

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GROUP psychotherapy is not a new method of treating social and mental maladjustment. Those who were distressed of spirit and were comforted by Christ, Confucius and other great teachers were guided by their leaders in a way of life primarily through group instruction. All teachers are, in effect, psychotherapists who impart knowledge whereby men may attain to wisdom and live more happily.

Class technic has been used in the treatment of many varied disorders. My personal introduction to effective group psychotherapy was under the tutelage of Dr. Joseph Walsh at the White Haven Sanitarium. The remarkable alteration in outlook and the creation of hope that Dr. Walsh effected in men and women at White Haven were striking, but the effect upon the symptom of cough was even more remarkable. Dr. Walsh described the effect of coughing on the lesions of tuberculosis, and encouraged the patients to control the impulse to cough. Older patients reminded newer ones to exercise such control and gave helpful suggestions; this participation in the program of each other's improvement created a splendid morale, and it was actually unusual to hear a cough in a sanitarium for the treatment of tuberculosis!

Later, at the Philadelphia General Hospital I participated in group instruction of diabetics and of cases of neurosyphilis in the out-patient department. I soon found that it was extremely helpful to have new patients called aside in small groups and informed of the nature of their condition and given renewed hope through assurance that treatment would be efficacious. As a consequence, many who regarded themselves as doomed because of having been told they had syphilis of the brain soon became encouraged and coöperative. These experiences dictated my decision to utilize group psychotherapy in the routine handling of psychoneurotics at the Presbyterian Hospital.

At the present time the most successful exponents of group psychotherapy as a means of treating the neuroses are Pratt [1] of Boston and his co-workers, Harris [2] and Rhoades.[3] Their work has been carried on for 10 years or more. Many others, among them Lazell [4] and Wender,[5] have reported experiences with group psychotherapy in a variety of conditions.

About a year ago we began the use of the group technic in the neurological department of the Presbyterian Hospital as a means of economizing on the staff's time and effecting more satisfactory results than were obtained by

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From the Neurological Service of the Presbyterian Hospital, Philadelphia, Pennsylvania.

brief, individual interviews. To this group were referred patients from the neurological and other dispensaries, patients whose complaints could not be demonstrated to have an organic basis and who were diagnosed as suffering from neuroses. The only requirements for referral to the group have been that the patients be intelligent, understand English, manifest some degree of willingness to coöperate in treatment, have no particularly objectionable traits, and are not too far advanced to be incapable of reacting emotionally.

The group has varied in size, with attendance ranging from six to 17. New members are admitted at any time during the year and are encouraged to continue, although about 20 per cent have dropped out. An effort has been made to have at least one new member report each week, since this gives us the opportunity of repeating certain fundamentals weekly without the older members of the group being aware that such repetition is for their benefit.

The setting of the classroom is decidedly informal, and no particular seating arrangement has been planned except that we have encouraged the older members and those who have received most benefit to take places in the front of the room. This they are rather anxious to do. The class usually opens by taking the roll of members, recognizing and commenting upon those who have been regular in attendance, and congratulating any returning backsliders. The next few minutes are devoted to the new members, and a brief statement is made pointing out to them the reason for their being referred to the class. As a rule, each of them has had a personal interview with the physician prior to admission to the group, but once again it is repeated they are being referred to the class because no evidence has been found that they are suffering from organic disease. An explanation is given of how their varied symptoms are the result of transient alteration of function of various organs, brought about by disturbance of nerve impulses as a result of anxiety or other emotion. Their attention is called to the sensations they may have experienced as a result of stage fright or other upsetting situations, and such sensations are compared to some of their symptoms. As a rule, most of the patients complain of some cardio-respiratory or gastrointestinal disturbance, so the effect of emotion upon the functioning of the gastrointestinal tract and cardio-respiratory system is forcefully explained. Veterans of the class are usually requested to tell in their own words how their emotions produced symptoms which at one time they were sure had been due to organic disease. Such recitals generally make a decided impression upon the newcomers.

After these brief and informal testimonials on the part of one or two members the effect of physical tension upon the nervous system is described. The patients are informed that when they are physically tense the nervous system is made far more receptive to emotional or other stimuli. They are then instructed in methods of relaxation. They are asked to assume the

most comfortable position possible, with the feet placed firmly on the floor and the hands at the sides or crossed comfortably in their laps. They are then directed to focus their attention upon a simple object in the front of the room, and in a somewhat monotonous voice the leader describes how their attention is being narrowed down to a few suggestions and to the object before them. As attention is fixed their minds become more tranquil and they begin to experience a comfortable sensation of heaviness and drowsiness. This type of suggestion usually leads to effective relaxation of the majority of the members, and some few have drifted into snoring sleep. On some occasions, instead of focusing attention on a single object, they are requested to visualize a scene which the examiner describes. A soothing, pastoral scene is then depicted and the patients are asked to signal when they visualize it completely. When they are lulled into a tranquil state by suggestion, encouraging statements and suggestions are repeated, and the dynamics of some particularly common symptom is usually discussed. Later, patients experiencing the particular symptoms under discussion are asked for comment. The discussion continues informally in this vein. Very frequently hypothetical cases are outlined and the patients are asked to submit written comments on the cases described. Quite often the cases are those of members who are present, and the following week as their case is discussed such individuals frequently enter into the discussion with great vigor. They are often requested to outline a plan or course of action for themselves which is argued pro and con by the group.

During the course of each session inspirational bits of poetry are quoted or some helpful comments are made, and those who have favorite phrases or bits of philosophy are urged to contribute their little gems. In the early weeks of the class few were able to supply any particularly inspiring phrases or quotations, but after a few weeks of attendance all of them sought to contribute inspirational messages which they considered precious. By this and other means each patient is made to consider himself an important member of the group.

When the class was newly formed, as might be expected, most of the patients remained aloof while waiting for the session to begin. Later on a spirit of friendship and mutual interest grew up among them, and now they arrive at the hospital earlier each week in order to have more time to discuss various subjects which they have in common. They have found the group a new forum that in every way satisfies their gregarious instincts.

The importance of symptom production through conflict is impressed upon the minds of the patients. It is pointed out that conflict cannot exist in the presence of understanding. We try to make them appreciate their physical symptoms on a pathophysiological basis produced by emotion. During all lectures free use of examples and parables is made. Many of the individuals in the group have had at least some contact with the misinter-

preted psychoanalytic concept of mental illness and have great difficulty adjusting the biological and the social. The duality of the personality in this respect is discussed, and the necessity of repression and harmonious compromise is emphasized. Man's gregarious nature is a topic of free discussion; primitive desires and urges with their effect upon behavior are also subjects considered. The desirability of the dominance of intellectually directed behavior over purely emotional reactivity is stressed. Efforts are made to have patients recognize the effect of resentment, bitterness and other destructive mental forces in the production of symptoms and to develop resignation, charity and finer qualities in their stead.

Thus far the number of patients treated in our group has been too small to warrant any statistical report, but among those who have had greater experience Harris [2] reported in 1939 that 68 per cent of the patients treated showed improvement varying all the way from complete freedom from all symptoms to lessening of one or two complaints. In our small group several patients have reported remarkable improvement of gastrointestinal, cardiac and other visceral symptoms, with relief of pain, headache and depression being also frequently experienced. Up to this time only one patient has discontinued attendance at the clinics because of complete recovery. At present she is employed and cannot attend, but letters of greeting to the group and good wishes to the leader and individual members have been written on several occasions. This patient appears to have undergone a complete change of personality. Several others are coming to the class less frequently; one, regarding herself as entirely well but appreciating the inspiration the class affords her, admittedly is attending only to help out with the newcomers.

In an analysis of the effects it is interesting to examine the mechanisms that make improvement possible. Unquestionably, since all members are requested to supply a detailed written recital of their symptoms and personal history, the mechanism of catharsis is an important one. There has been definite evidence of the mechanism of transference, and there is no doubt that some element of rivalry for the attention of the leader has effected improvement. After a few sessions most of the patients begin to feel of some importance since their opinion is asked in discussion of the emotional difficulties of another member or hypothetical individual. Unconsciously they begin to apply some of the suggestions to themselves. There is little question that in the group " mob psychology " produces many of the results, and at certain of the sessions it has been apparent that a comment by a member is taken up by others and regarded as a gem of wisdom to which they promptly give allegiance and report benefit therefrom. It is interesting to note that when the group reconvened after a vacation of four weeks, they seemed to outdo each other in their desire to report great improvement.

Summary and Conclusion

The group method of treating the psychoneuroses is one that affords a partial solution of the problem of the psychoneurotic in the large urban hospital. The same technic and mechanisms that are applied to the management of the individual can be applied in dealing with the group. The organization of such classes for the management of the neuroses would, I feel, be an effective method of combating cults and quacks. With a little common sense and conviction any individual, regardless of personality, should be able to effect benefit through the group management of the psychoneuroses. I visualize the method as one that would be of great value in combating war neuroses.

REFERENCES

1. Pratt, Joseph H.: The influence of emotions in the causation and cure of psychoneuroses, Internat. Clin., 1934, iv, 1–16.
2. Harris, Herbert I.: Efficient psychotherapy for the large outpatient clinic, New England Jr. Med., 1939, ccxxi, 1–5.
3. Rhoades, Winfred: Group training in thought control for relieving nervous disorders, Mental Hyg., 1935, xix, 373–386.
4. Lazell, E. W.: The group psychic treatment of dementia praecox by lectures in mental reëducation, U. S. Veterans Bureau Bull., 1930, vi, 733.
5. Wender, Louis: The dynamics of group psychotherapy and its application, Jr. Nerv. and Ment. Dis., 1936, lxxxiv, 54.

THE RÔLE OF THE VERTEBRAL VEINS IN METASTATIC PROCESSES *

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Miliary tuberculosis, erysipelas, and tuberculous adenitis have lesion-patterns characteristic of diseases spread by blood and lymph vessels. These three diseases represent three types of spread. In miliary tuberculosis, the arterial blood stream distributes multiple foci at random. In erysipelas, organisms invade a plexus of lymph vessels and multiply. As a result the primary lesion enlarges, colony-like, from its margins. In tuberculous adenitis, the organisms spread in lymph vessels to multiply in the regional lymph nodes and lymph node chains. Modifications of the typical patterns are common. For example primary lesions in the left side of the heart, or in the lungs, may give rise to solitary, instead of multiple artery-borne secondary foci. An erysipelas-like lesion may appear atypical because of markedly irregular margins. A lymph gland chain may be only partially involved by disease and as a result the disease-pattern may appear discontinuous. These three lesion-patterns require only the classical, elementary concepts of a blood and a lymph system to explain their sequence.

Several diseases with primary and secondary lesions, particularly tumors, do not spread in the simple patterns noted above. The tumor metastatic patterns receive more attention than the patterns of infectious metastases, but the problem of spread of either sort of a metastasis is the same. The schema outlined above does not account for the high incidence of brain abscesses secondary to lung abscesses. If these brain abscesses develop from solitary, artery-borne emboli, why should the brain be so frequently the site of lodgment? The suggestion that the relation of the carotid arteries to the aortic arch is responsible for this frequency does not bear scrutiny—the secondary lesions occur in the brain only, not in other areas of the head supplied by the common carotid arteries. Carcinoma of the breast spreads to the other breast, to the ribs, to the vertebrae, or to any of these, and yet the lungs can remain free of disease. This non-involvement of the lungs is hard to explain if metastatic emboli must go from the breast to the right heart, to the lungs, and to the left heart before reaching the secondary foci noted above. Even an open foramen ovale has been called upon to explain this paradox. These " aberrant " metastases occur in as high as 40 per cent of cases.[1] Lung capillaries too large to filter out cells in their passage through the pulmonary circulation have been suggested.[2] Careful workers (Walther,[3] Willis [4]) find microscopic carcinoma lesions in many lungs which might seem to indicate that no actual paradox exists. These interesting find-

* Read at the Boston meeting of the American College of Physicians, April 21, 1941.
From the Graduate School of Medicine, University of Pennsylvania.

ings do not wholly clarify the problem. It is necessary to know whether these microscopic lung lesions preceded, occur concurrently or follow the larger metastases. The microscopic size, suggesting a young lesion, may indicate a tertiary lesion, i.e. one due to spread from a metastasis.

Handley [5] devised the theory of permeation of the lymph vessels by tumor cell growth to explain the vagaries of spread of carcinoma of the breast. In brief, Handley's theory explains lesions at a distance by supposing an extensive erysipelas-type of a spread with the disappearance of the disease trail in the tissues between the primary and secondary sites. This theory is difficult to fit to a case of primary tumor in the left breast with a solitary metastatic lesion as remote as the right frontal bone.

Prostatic carcinoma spread requires special consideration. The definite diagnosis of primary prostatic carcinoma is frequently first made by the roentgenologist on finding metastases in the pelvis. The metastatic pattern, so characteristic as to warrant a positive diagnosis, is wholly unlike the pelvic lymph chain pattern. It seemed to me to resemble the vein plexus pattern. The spread of prostatic carcinoma cells through the pelvic veins would fit with the recent trend of thought. Walther,[3] Willis,[4] and others, believe that carcinomas spread by the lymphatic system only so far as the regional lymph nodes—from there on the blood vascular system is the carrier.

The route of spread from the prostatic veins was studied by injections made in cadavers and in living monkeys. These and other vein injection studies have been reported in part (Batson [6]). In making the injections, advantage was taken of the fact that the deep dorsal vein of the penis is practically an integral part of the prostatic plexus of veins. (Figure 1.)

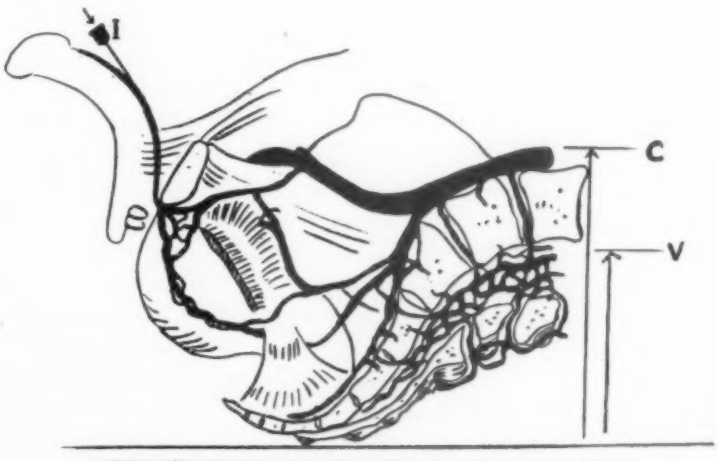

FIG. 1. Diagram of the pelvic veins in a lateral view. *I*, the point of injection of the deep dorsal vein of the penis. Note the alternate routes by which the veins ascend the body. The difference between the height of the vena cava, *C*, and the vertebral vein plexus, *V*, is indicated by the arrows. This explains the ready filling of the vertebral plexus when the cadaver is in the dorsal recumbent position.

Injection of roentgen opaque substances into this vein in the cadaver was followed in roentgen films. A thin injection mass did not flow into the inferior vena cava but spread into the veins of the bones of the pelvic girdle and the veins in the vertebrae and those about the vertebral column, giving a replica of the spread of prostatic carcinoma. These are the veins first, and so well described by Breschet [7] over 100 years ago. By adjusting the viscosity of the injection mass to the resistance of the vessels of various sizes the amount of injection mass to reach the inferior vena cava can be controlled. This is due to the fact that the vena cava is at a higher hydrostatic level than the vertebral veins, when the cadavers are in the dorsal recumbent posture. (Figure 1.) By increasing the quantity of mass injected the material reaches the brain. These experiments demonstrated a set of valveless, plexiform, longitudinal, venous channels that join the cranial venous sinuses to the pelvic veins without the intermediation of the lungs.

Injections of the living monkey indicated the probable sequence of events in the spread of metastases. Upon injection into the dorsal vein of the penis of the monkey the roentgen opaque material coursed to the inferior vena cava. This unquestionably is the normal course of flow in the living. When, however, the increased intra-abdominal pressure of straining was simulated by tying a towel around the monkey's abdomen, the injected material met resistance to passage through the vena cava and ascended the bone-protected vertebral vein plexus, and from there spread out into several intercostal vessels. This great network of veins around the spinal dura mater and the vertebrae serves as a venous pool or lake. It is of particular physiologic significance during the compression of the chest and abdomen in coughing, lifting, and straining.

The spread of injected material from the prostatic veins suggested the study of the spread from the breast veins. Here it was found that by the injection of a small breast venule in a cadaver the veins of the shoulder girdle, head of the humerus, thoracic vertebrae, neck, and brain were visualized in roentgenograms. The material, to be sure, also ran into the superior vena cava. Here was a pathway from another region to adjacent and remote parts, through a valveless network of veins that did not lead through the lungs. This network is a part of the same network that was filled by injecting the prostatic veins. It was suggested, therefore (Batson [6]), that all of the veins of the trunk wall, which would include the breast veins, all of the veins of the head and neck, the major *venae vasorum* of the vessels of the extremities, and the veins of the vertebral column (the vertebral veins, *sensu strictu*), be considered a separate vein system, to be called for brevity "the vertebral vein system." This vertebral vein system parallels the portal, the caval, and the pulmonary vein systems, providing a by-pass around these systems as well as serving as a venous pool during compression of the body cavities. This concept of a vertebral vein system clarifies many of the

"paradoxes" of metastatic spread; it does not supersede but rather complements concepts well founded upon obviously adequate evidence.

I have had experience with over 100 anatomic injections, since the first report, summarized above. We now inject as an anatomic laboratory routine the deep dorsal vein of the penis of all male cadavers. Studies of the spread of material injected into the veins of the female breast have likewise been extended. Through the discussions of colleagues additional clinical applications have been brought out. This increased experience and the discussions permit additional comments to be made and some questions to be answered. Since the breast vein injections have been especially illuminating they will be described in detail.

In our routine cadaver injection we have used a colored latex emulsion. More recently a roentgen opaque medium has been added to this latex so that it is possible to follow the injection radiographically as well as visually. In the large number of cadavers that we have been able to observe, the variety and number of connections that exist between the caval system of veins and the vertebral vein system have become impressive. It is obvious that such valves as are present in the vertebral vein system are as a rule incompetent in later adult life. This has been previously noted by Franklin [8] and others. In our routine injections of the deep dorsal vein of the penis we expect to obtain a fairly complete injection of the cerebral veins in 7 out of 10 cases. This is a very high proportion of successes for any routine injection technic and indicates the free communications present. Frequently the subpapillary venous plexus of the skin of the face is also injected. (Figure 2.)

The variety and number of connections between the caval and the vertebral vein systems are also to be noted during the course of a surgical laminectomy. The neuro-surgeon expects to see epidural veins fill and empty with each respiratory cycle. The slight changes in intra-thoracic pressure are sufficient to cause filling and emptying of the epidural veins through the multiple large connections. The total mass of vessels in the vertebral vein plexus becomes the more obvious the greater the number of injected anatomic specimens examined. It is assumed that any group of veins with a capacity for carrying more blood than the region requires is serving as a venous reservoir or lake. The vertebral vein system is therefore an enormous venous lake. It would appear possible for an embolus to remain for an indefinite period in this plexus of veins without being propelled into the heart. Regularity of direction of flow through a reservoir of this size is difficult to imagine. The direction must shift with each rise and fall of pressures at the communicating vessels, sometimes going toward the caval system of veins and sometimes longitudinally, either up or down. Solitary emboli, malignant or infectious, would likewise be propelled toward the heart or along the longitudinal extent. The same would be true for showers of emboli.

It has been objected, that according to this concept of spread, metastases

should invade the spinal cord as frequently as the brain. This sparing of the cord should be expected from the anatomy of the vertebral veins themselves. The small spinal cord veins pierce the dura and flow into the extradural plexus at right angles. The enormous main network of vertebral veins has in general a longitudinal course. These longitudinal vessels terminate cranially at the foramen magnum in the great venous dural sinuses. In brief the spinal cord is connected by small vessels to the vertebral vein plexus;

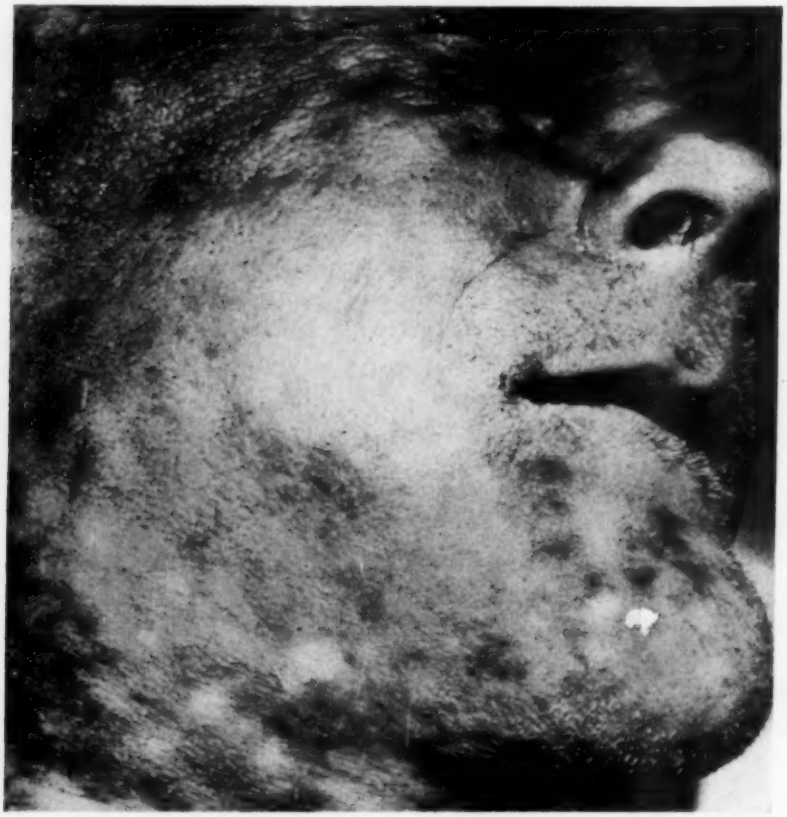

FIG. 2. Photograph of the face of a cadaver after the injection of the deep dorsal vein of the penis. The injection by extending from the deep veins into the subpapillary plexus of the skin has produced the well marked mottling.

the cerebral venous dural sinuses are themselves the direct cranial continuation, in fact the terminus, of the vertebral vein system.

To this point we have considered the distribution of solitary and multiple emboli without the necessity of passage through the lung. The breast vein injections have suggested another type of spread by veins. To inject these breast veins it is necessary to use very small cannulae. A lachrymal cannula is most effective. Weber's water color vermillion, diluted to a watery

thinness, makes a good roentgen-opaque mass. India ink is satisfactory for visual observation. The injection of roentgen-opaque material is followed during injection with the fluoroscope. As much as 30 c.c. has been injected into the plexus of breast venules before the material was seen to flow into the intercostal or axillary vessels. While 30 c.c. is an unusual amount, 10 c.c. to 20 c.c. can commonly be injected into this sub-papillary venous plexus. These subcutaneous vessels are of more or less uniform size and exist in a branching and intercommunicating network. They are valveless. I have seen (figure 3) as small a quantity as 8 c.c. cause a suffusion of color into multiple areas of both breasts. No barrier exists at the midline. (Figure

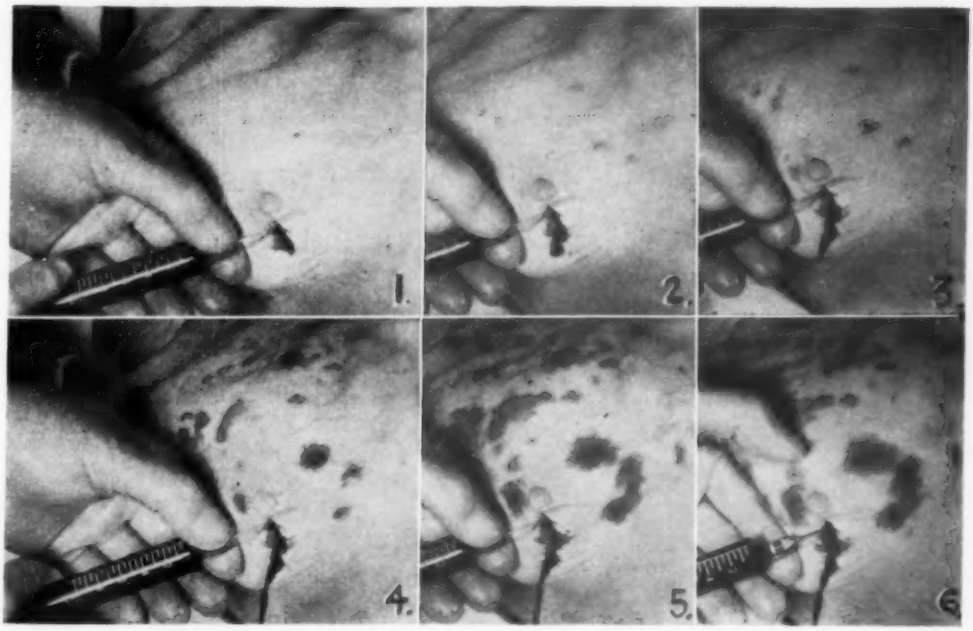

FIG. 3. Six photographs from the motion picture record of the injection of a venule in the right breast of a female cadaver. Nos. 1, 2, 3, and 4 show the injection of 8 c.c. of India ink. No. 5 shows the effect of increasing the amount of injection and No. 6 the specimen after the total of 24 c.c. had been injected. No resistance to injection was encountered.

4.) These vessels are in sharp contrast to the lymphatic vessels with their small caliber and many valves. This venous network could be a route over which metastases spread, as well as the lymphatic plexus emphasized by Handley.[5] The entire pattern of the vein injection reminds one of *carcinoma en cuirasse*. Permeation of the subpapillary plexus of veins may be of greater importance than the permeation of lymphatics.

The anatomy of the veins, therefore, provides a mechanism for understanding both paradoxical emboli and skin permeation as in breast cancer. These concepts do not minimize the invasion of the lymphatics by carcinoma cells nor the direct spread along these lymphatic channels to the regional lymph nodes. The spread by veins, however, probably accounts for the very

rapid dissemination which can occur across the midline, for example, to the opposite breast.

The technical difficulty of the demonstration of the central plexus of this vertebral vein system has delayed the appreciation of its rôle in the normal

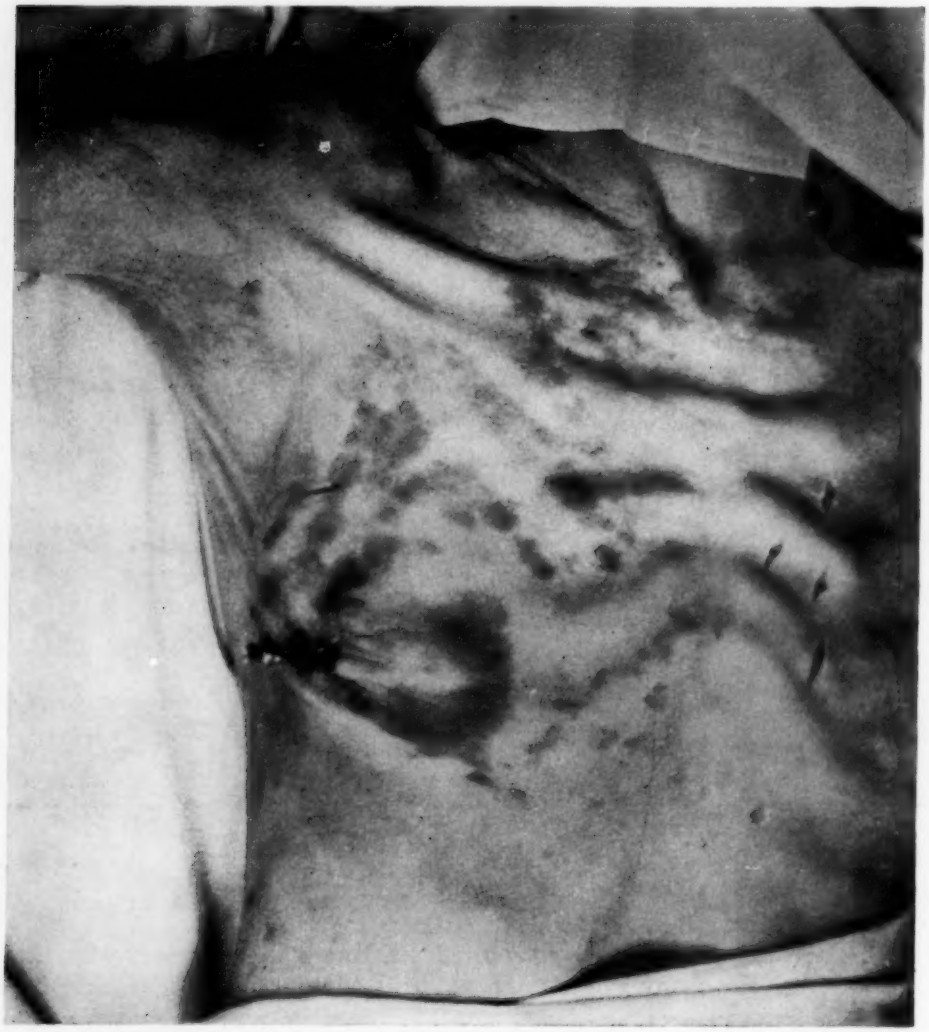

FIG. 4. Same cadaver as in figure 3. This view shows the extensive distribution of injected material to the opposite breast, the supraclavicular regions and the axillary fossa. The short vertical incisions on the left chest disclose the subcutaneous veins filled with the ink. The ink was also found in the cranial dura mater.

and pathologic economy of the body. Once the significance of these veins as a vein system is clear, many applications are possible. Hadden,[9] for example, has noted the relationship of this vein system to the condition known as Spiller's ascending paralysis. Further, introduction of air into these veins

would account for the blindness and even death which sometimes follows the diagnostic perirenal insufflation of air or air injections to produce pneumothorax. Taylor [10] reports a case which he relates to the vertebral vein system. Several hours after an operation for empyema a woman patient collapsed and died. A careful autopsy disclosed air emboli in the large dural sinuses, none elsewhere, and no other significant findings. Taylor reasons that the air went from the empyema cavity into the azygous vessels and then by way of the vertebral vessels to the cerebral sinuses. Anoxia from the air emboli blocking the mouths of the Rolandic veins seems to have been the cause of death.

The ocular palsies accompanying incisional abscesses of the abdominal wall may depend upon emboli reaching the cranium through this system. The full significance of this venous route will be realized only when it is regularly examined at the autopsy table.

Summary

The vertebral vein system consists of the epidural veins, the perivertebral veins, the veins of the thoraco-abdominal wall, the veins of the head and neck, and the veins of the walls of blood vessels of the extremities. It is a set of valveless vessels which carries blood under low pressures. In the subcutaneous tissue the smaller vessels provide a continuous network permitting ready permeation. Around the vertebral column the vascular bed of the system is much larger than required by the parts in which it is found. It is a system which is constantly subject to arrests and reversals in the direction of the flow of blood. The vertebral vein system parallels, connects with, and provides by-passes for, the portal, the pulmonary, and the caval systems of veins and hence can provide in itself a pathway for the spread of disease between remote organs.

BIBLIOGRAPHY

1. Willis, Rupert A.: The spread of tumors in the human body, 1934, J. & A. Churchill, London, p. 321.
2. Walther, Hans E.: Untersuchungen über Krebsmetastasen, Ztschr. f. Krebsforsch., 1937, xlvi, 313–333.
3. Walther, Hans E.: Der Nachweis sekundärer Knochengeschwülste, Radiol. Clin., 1939, viii, 69.
4. Willis, Rupert A.: Personal communication.
5. Handley, W. S.: Cancer of the breast and its treatment, 1922, London.
6. Batson, Oscar V.: The function of the vertebral veins and their rôle in the spread of metastases, Ann. Surg., 1940, cxii, 138–149.
7. Breschet, Gilbert: Récherches anatomiques, physiologiques et pathologiques sur le système veineux et voie anatomiques, 1832, Paris.
8. Franklin, Kenneth J.: A monograph on veins, 1937, Charles C. Thomas, Springfield, p. 77.
9. Hadden, Samuel B.: The rôle of increased intra-abdominal and intrathoracic pressure in the production of the demyelinization and degeneration in the spinal cord, Presidential address, Philadelphia Neurological Society, February 1941.
10. Taylor, Stephen: Spread of paradoxical metastases, Lancet, 1940, 638.

A STUDY OF THE HEREDITARY NATURE OF GOUT; A REPORT OF TWO FAMILIES *

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STIMULATED by the observation of gout in several members of one family we have made a systematic study of all of the immediate relatives of two gouty individuals in order to determine the importance of heredity as a factor in the etiology of this disease. In the vast amount of literature on the subject of gout and uric acid, reports of *proved* cases of gout in near relatives of patients in whom the diagnosis of gout has been established are sufficiently rare to make this study valuable. As far as can be determined, this is the first systematic investigation of the serum uric acid values in the immediate members of gouty families.

For many centuries it has been recognized that gout is very probably an hereditary disease. However, references to the subject usually contain only fragmentary data concerning the family histories. Scudamore,[1] in 1819, mentioned a butcher who could not trace gout to any former generation in his family but had three brothers who suffered greatly from the disease. This same writer observed a man with two sons and a daughter, out of five children, with severe gout, and another family of which the father, mother and all sons and daughters, four in number, had gout. He also noted confinement of this disease to only one or two members of large families. For example, out of 14 children only one brother and one sister had gout; in another family of 10 children with a gouty father only one son was afflicted. Garrod,[2] in 1931, observed a man who had his first "orthodox gout" in the great toe at the age of 20; his father, paternal grandfather, two brothers and three sisters all suffered from "true gout" and in a son of one of his sisters gout began at the age of 16 years.

It has been stated by many observers [1, 2, 3, 4, 5, 6] that in from 50 to 60 per cent of all cases of gout there is a history of the disease in the parents or grandparents. These figures are based upon the patients' statements only and from the reports it appears that no attempt was made to verify the diagnosis by examining the relatives. Therefore, the accuracy of such statements is subject to considerable criticism. In the first place, it is well known that in gouty families the disease may skip several generations and, therefore, history of the malady occurring in ancestors may be elicited only by diligent inquiry, if at all. Very few people are able to give an exact

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From the Rackham Arthritis Research Unit, the Medical School, University of Michigan, Ann Arbor.
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account of the ailments of their grandparents or great-grandparents. Furthermore, there can be little doubt that in the light of our present criteria for diagnosis many cases included in these early reports were probably diagnosed incorrectly. Many errors in diagnosis must have been made before modern laboratory methods for determination of blood uric acid concentration, and for proving the existence of tophi by chemical and histologic tests were available, and before diagnostic roentgenograms were employed. These early reports are valuable, therefore, only in that they suggest the hereditary tendency of the disease; they do not permit an accurate analysis nor do they indicate the mode of transference of the hereditary tendency.

The first study of blood uric acid values in an apparently healthy relative of a gouty patient known to us, is that of Folin and Lyman [7] in 1913. They found an elevated blood uric acid value in a man "in whose family there had been more or less gout." This observation was apparently recounted subsequently (1915) by Folin and Denis.[8] The only other similar observations of which we are aware are contained in the more extensive report of Jacobson (1938).[9] He found serum uric acid values definitely elevated in three "normal" males, all close relatives of three different gouty patients. Findings in other members of these families were not reported.

Garrod [2] has pointed out the need for studies of the uric acid concentration of the blood of members of gouty families from infancy upwards in order accurately to evaluate the importance of heredity in this disease.

Method

In this investigation we have studied each immediate member of the families of two gouty patients, a total of 29 individuals. Besides attempting to detect the presence or absence of gout by history and physical examination, in all of the adults serum uric acid content was determined. Venous blood, obtained in practically all instances after a 12 hour fast, was immediately placed under oil, allowed to clot, and the serum analyzed by the indirect method of Folin.[10] By this method normal individuals have serum uric acid values of less than 6 mg. per cent so that values greater than this have been considered abnormally high. In many cases diagnostic roentgenograms of joints were made.

Report of Family I

The genealogy of the first family investigated is illustrated in chart 1. The presence of gout has been established in the father and his three sons. The only members not completely studied are related by marriage or are children under five years of age. We were very anxious to determine serum uric acid content in these children but were unable to gain permission to do this. None of these children have had joint symptoms.

The serum uric acid values are shown in table 1. In the four instances indicated by the asterisk the values are not during a fasting state.

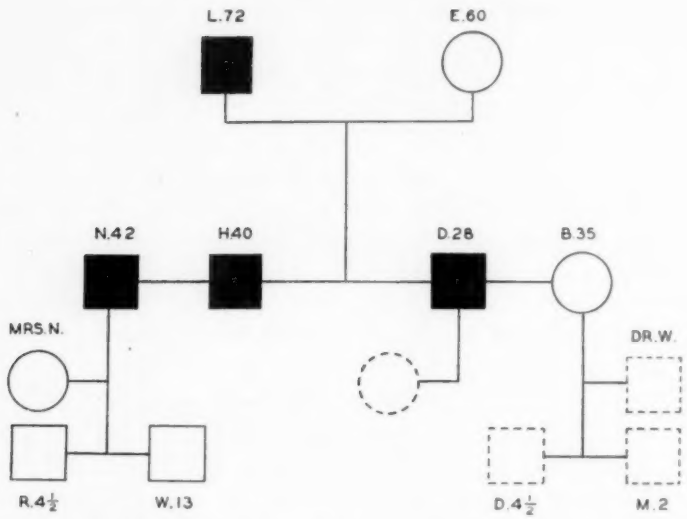

CHART I. An analysis of Family I. The squares represent males and circles, females. Proved cases of gout are shown in black. The letters signify the name and the numbers, the age of each member. The dotted squares and circles represent members without uric acid studies.

TABLE I

Serum uric acid values in members of Family I, in all cases determined during fasting state except where indicated by asterisk.

	Date	*Serum Uric Acid* mg. per cent
L. W. (Father)	10/16/39	7.9
	10/12/39	8.08
	12/16/39	9.2
E. W. (Mother)	10/12/39	6.06
	12/16/39	5.3
H. W. (Son)	9/19/39	8.89
	9/22/39	9.8
	10/ 6/39	10.0
	12/16/39	7.6
N. W. (Son)	10/12/39	11.43
	11/11/39	9.8
	11/28/39	9.8
D. W. (Son)	1/19/40	*10.2
B. W. (Daughter)	1/19/40	*5.7
N. W., Mrs. (Daughter-in-law)	11/11/39	3.87
W. W. (Grandson)	10/12/39	4.70
R. W. (Grandson)	10/12/39	4.44

Case histories of the four men, in whom the diagnosis of gout has been made, follow.

Case 1. L. W. (father), aged 72 years, Jewish, machinist. At the age of 42 years for the first time he had a sudden attack of severe pain accompanied by signs of inflammation sharply localized about each great toe. He was confined to bed for five weeks. Recovery was complete without any residual abnormality. Six months later, without any apparent cause, another similar attack occurred. Since that time he has had repeated bouts of joint pain, usually located in the feet and most marked in the region of the metatarsophalangeal joint of the great toes. During each attack all of the characteristic signs of acute inflammation develop. The duration of each attack has varied from a number of hours to three weeks. Hot packs and salicylates usually gave temporary and only moderate relief. During the past 10 years the attacks have occurred more frequently, about one each month, and no longer completely subside; during the last two years he has had pain almost constantly in the shoulders, right second metacarpophalangeal joint, knees, and ankles. For several years he has noticed small chalk-like deposits in both ears. These occasionally ulcerate and from them a granular, gritty material exudes.

His father lived to the age of 80 years and to the patient's knowledge, had never been troubled with joint disease. He did not know anything about his grandfather, aunts or uncles. He has one living sister, seven years his senior, who has never had any joint symptoms.

Physical Examination: There were typical tophi in the ears (figure 1). One

FIG. 1. Right ear of L. W., father of Family I, showing small ulcerated tophus from which sodium urate crystals were demonstrated.

tophus on the right ear was ulcerated and from this crystals of sodium urate were demonstrated; the murexide test was positive. The right first metatarsophalangeal joint was slightly swollen, tender, and painful and in it motion was moderately reduced. The right second metacarpophalangeal joint was slightly swollen and tender.

Laboratory Data: The fasting serum uric acid value was repeatedly elevated (table 1). Sugar was found in two of three urine samples examined. By the Shaffer-Somogyi method the fasting blood sugar was found to be 116.5 mg. per cent, which we consider slightly elevated. A tophus was removed by taking a wedge-shaped section from the left ear, and sections prepared according to the method of De Galantha [11] contained sodium urate crystals. Roentgenograms of the feet showed extensive changes in many joints; large cystic and punched out areas characteristic of the late stages of gout were present (figure 2).

Diagnoses: Typical tophaceous gout, questionable diabetes mellitus.

Case 2. N. W. (son), aged 42 years, married, came to the Arthritis Unit at our request. His chief complaint was attacks of multiple joint pains which he had had for 13 years. Early in the course of the disease the attacks occurred only every two or three years; in recent years, however, they occurred about every four months, and they persisted considerably longer than in the early stages of the disease. The attacks begin suddenly with extreme pain shortly followed by swelling, redness and increased heat, and were most often located at the metatarsophalangeal joint of the right great toe. The ankles, knees, and elbows have been similarly affected. These bouts of pain occurred most frequently in the fall and spring and were not related to exposure or over-indulgence in food and alcoholic drink. Various forms of therapy

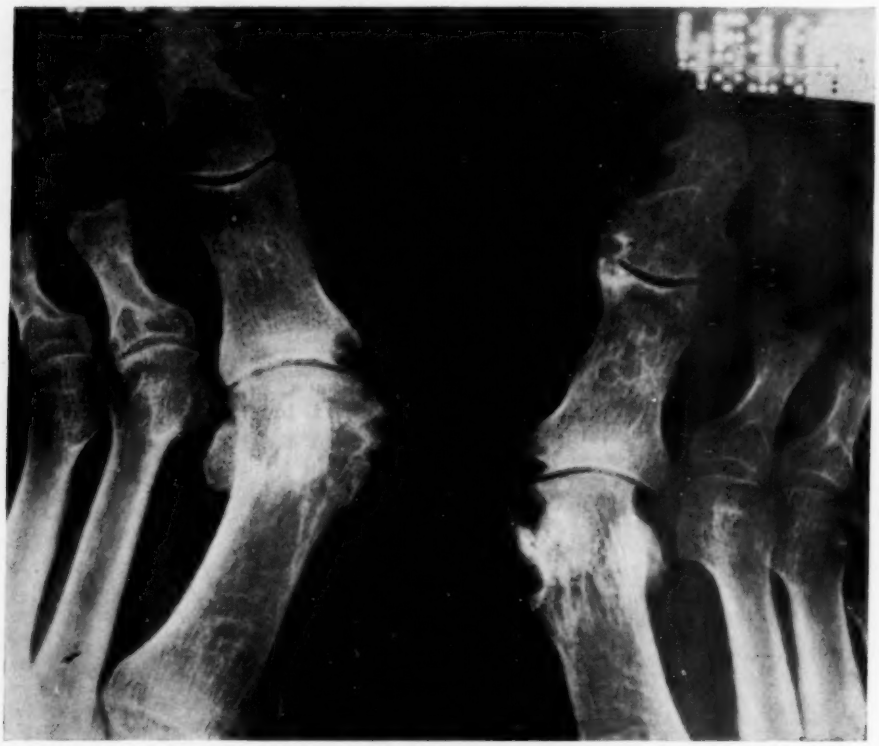

FIG. 2. Roentgenograms of L. W., father, Family I, showing multiple punched out juxta-articular lesions in toes.

had been instituted, including fever induced by "fever cabinet" and injections of sulfur. During the first attack only he took colchicine in whiskey which gave almost immediate relief.

Physical Examination: The only abnormality was slight tenderness over the right first metatarsophalangeal joint.

Laboratory Data: Repeated fasting serum uric acid values were elevated (table 1). The erythrocyte sedimentation rate was 0.95 mm. per minute (Ernstene-Rourke method). Roentgenograms of both feet showed small rounded areas of rarefaction along the proximal phalanx of the right great toe, and along the lateral margin of the head of the right first metatarsal bone (figure 3).

Diagnosis: Chronic gout.

He was advised to eat a low-purine diet, and when last seen had been asymptomatic for three months.

Case 3. H. W. (son), aged 40 years, single, was the first member of this family studied. He had had repeated attacks of pain in the ankles and right great toe for 10 years. Each attack began suddenly and the pain was so severe that weight bearing was impossible. Slightest pressure over the affected joints produced almost unbearable discomfort. At first these bouts of pain occurred once a year but they became more frequent and during the last two years he has had six attacks. They frequently follow sharp decreases in environmental temperature. Each episode has lasted from one to seven days. Although early in the course of the disease he was entirely free of symptoms between attacks, during the last three months he had almost constant aching pain in the ankles and has had occasional pains in the left wrist unaccompanied

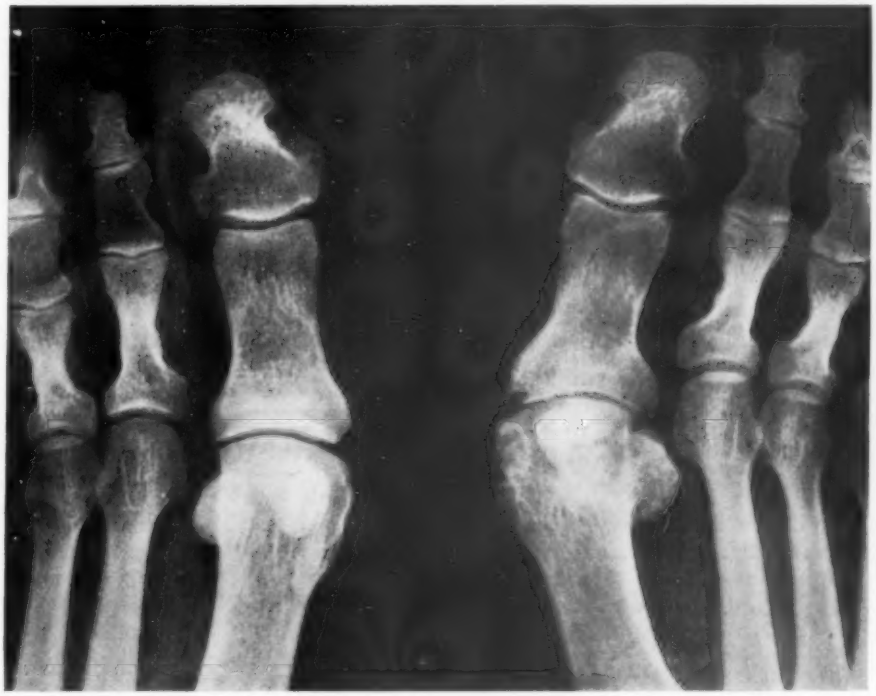

FIG. 3. Roentgenograms of N. W., son, Family I, showing punched out juxta-articular areas at the metatarso-phalangeal joints of each great toe.

by evidence of inflammation. Through his coöperation all other immediate members of this family have been studied.

Physical Examination: Entirely negative.

Laboratory Data: Numerous uric acid values were significantly elevated (table 1). Two urinalyses showed no abnormalities and the hemoglobin and complete blood counts were normal. The erythrocyte sedimentation rate on two occasions was 0.40 mm. per minute (Ernstene-Rourke method). Roentgenograms of the ankles, feet and wrists showed only slight changes.

Diagnosis: Pre-tophaceous gout.

An attempt was made to induce an attack of gouty arthritis by the use of a high fat diet according to the plan suggested by Lockie and Hubbard.[12] A diet com-

posed of 50 gm. of protein, 160 gm. of fat, and 45 gm. of carbohydrate was eaten for two weeks, during which time no increase in joint symptoms occurred; in fact, the ankle pain almost completely disappeared. Since this time he has been eating a low-purine diet and has been free of symptoms.

Case 4. D. W. (son), aged 28 years, married. This person was visited in his home, and he reported that he had had one attack of severe *podagra* during each of the last five years. Each attack had a sudden onset of pain, soon followed by all of the signs of acute inflammation. The shortest attack had been two days and the longest 11 days. He had had no symptoms for five months. No tophi were found and the joints showed no physical abnormalities. His physician informed us that he had examined the patient during one of his attacks and considered it to be typical of gout. A non-fasting serum uric acid value was 10.2 mg. per 100 c.c. (table 1).

Diagnosis: Pre-tophaceous gout.

The other members of this family who have been examined show no positive evidence of gout. In the case of E. (mother) the first serum uric acid value obtained was 6.06 mg. per cent (borderline); the second determination revealed a value of 5.3 mg. per cent. The blood non-protein nitrogen content at this time was 35 mg. per 100 c.c. The only daughter in this family had no history of joint disease; her serum uric acid value was 5.7 mg. per cent (non-fasting). The two grandsons who were examined exhibited no evidence of gout.

Report of Family II

The father of this family has chronic gout. Two sons have significantly elevated serum uric acid values, another son has a high normal value, and the only daughter has an average normal value (table 2). None of these children have had symptoms of gout at any time. We were unable to obtain blood for uric acid analysis from any of the grandchildren, all of whom are under five years of age. The genealogy of this family appears in chart 2.

Table II

Serum uric acid values in members of Family II, in all cases determined during fasting state except where indicated by asterisk.

	Date	*Serum Uric Acid* mg. per cent
F. B. (Father)	11/27/39	7.27
	11/14/39	7.02
	11/14/39	8.60
N. B. (Mother)	11/27/39	3.69
R. B. (Son)	11/16/39	7.94
D. B. (Son)	11/27/39	8.42
C. B. (Son)	11/27/39	5.60
G. B. (Daughter)	1/19/40	*4.3

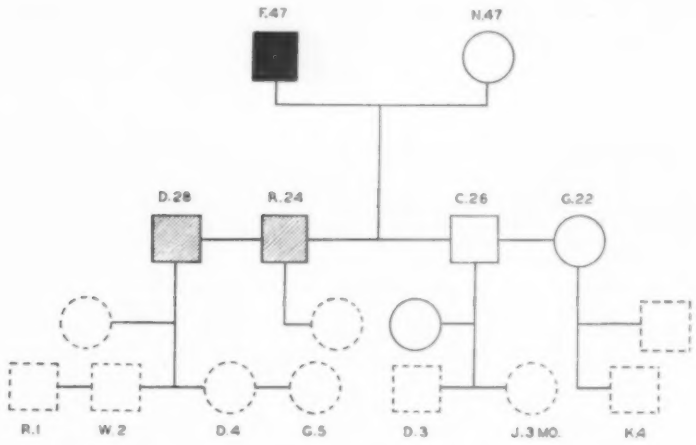

CHART II. An analysis of Family II. The squares represent males and circles, females. The solid black square indicates the existence of proved gout. The shaded squares indicate members with significantly elevated serum uric acid values. The letters and numbers signify the name and age of each member. The dotted squares and circles represent persons without uric acid studies.

The case history of the father follows:

F. W., aged 47 years, steel mill worker, was able to recall the exact date of his first attack of joint pain—October 27, 1933—when sudden sharp pain developed in the right great toe. He was unable to walk for five weeks. The attack completely subsided without residual deformity or tenderness. One year later a similar attack occurred in the same joint and, in addition, the right ankle was similarly affected. With each attack the involved joints have been greatly swollen, red, and hot and at that time even the slightest pressure caused almost unbearable pain. Two years after the initial episode another attack occurred which lasted five weeks and which was similar to the first two. In May, 1939, the fourth attack occurred, which affected the right shoulder and knee, the left elbow, wrist and hand, in addition to the right great toe and ankle. Soreness persisted in all of these joints throughout the summer and fall of 1939 and an acute exacerbation occurred three weeks before his admission to this hospital, November 15, 1939.

Physical Examination: He was moderately overweight, apparently comfortable and could bear his full weight on both feet. No tophi were found. The left wrist was swollen, tender, painful and moderately limited in motion. The skin over the dorsum of the left hand and wrist was moderately cyanotic. The right knee was slightly swollen and contained an increased amount of synovial fluid. The right great toe was slightly tender at the metatarsophalangeal articulation.

Laboratory Data: Repeated serum uric acid determinations have on each occasion shown high values (table 2). Synovial fluid and blood serum removed simultaneously contained 8.6 and 8.4 mg. of uric acid per 100 c.c. of fluid respectively, and each fluid contained the same (low) amount of vitamin C, i.e., 0.34 mg. per cent (Farmer-Abt method, 1935). The erythrocyte sedimentation rate was 1.0 mm. per minute. There was a small erosion of the head of the left first metatarsal bone shown in the roentgenogram (figure 4).

Diagnosis: Chronic gout.

He was given colchicine 0.0005 gram (1/120 grain) hourly for eight hours and following the fourth dose there was a marked improvement in his symptoms. After

two days slight stiffness of the left wrist was the only abnormal physical finding. He was instructed to eat a low-purine diet and discharged from the hospital. When seen five months later he reported that he had had no joint symptoms during this interval.

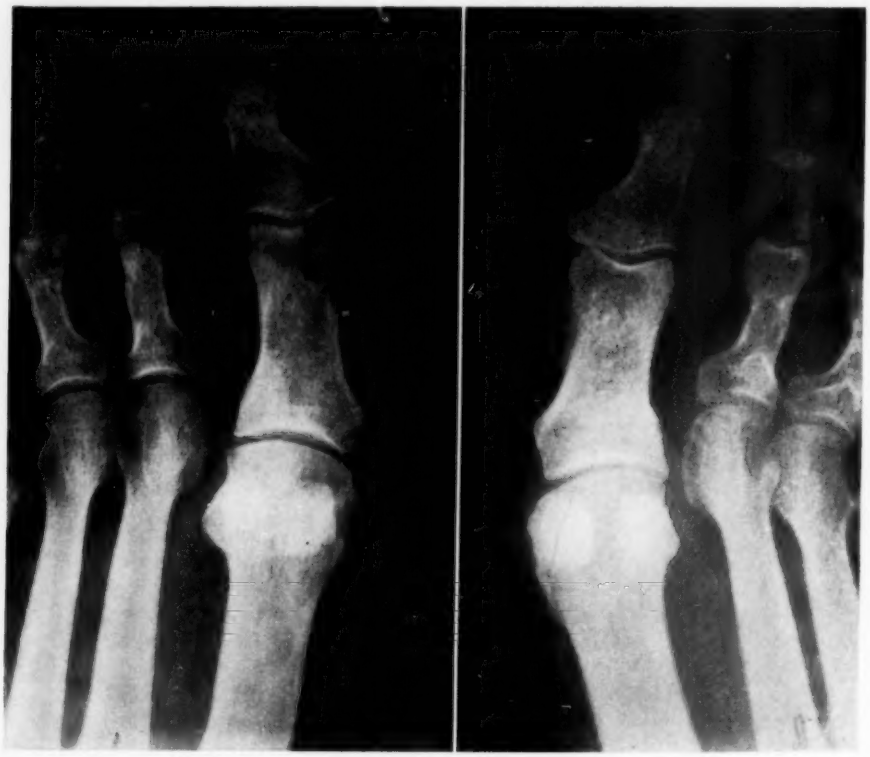

FIG. 4. Roentgenograms of F. B., father, Family II, showing a small area of erosion at the head of the left first metatarsal bone.

DISCUSSION

In the two families that form the basis of this report all but one of the adult male members (eight) have gout or have elevated serum uric acid values, whereas all of the adult female members (four) have had no symptoms of gout and no hyperuricemia. These findings are in agreement with many other reports that this disease occurs primarily in males. At present there is no adequate explanation for the disproportionate occurrence in males, but this fact suggests that gout may be transmitted as a sex-linked hereditary factor. However, in another disease *known* to be hereditary with sex-linked transmission, i.e., hemophilia, only alternate generations suffer from the disease even though members of both sexes of the unafflicted generation transmit the hereditary tendency of the disease. Our data show that gout exists in successive generations, which is strong evidence against its being transmitted as a sex-linked character.

It has been suggested by Bauer, Fischer, and Lenz [13] and by Garrod [2] that the predisposition to gout is inherited as a simple dominant character and is transmitted according to Mendel's laws. If this be true, one would expect the disease to appear in *every* generation since it is impossible for a dominant factor to be present in the germ-cell and its effect not be manifested. The fact that in gouty families the disease may skip one or two generations and then reappear requires explanation if gout is transmitted as a dominant mendelian factor. Garrod [2] explains this by suggesting that persons inherit the susceptibility to gout which in itself is not detrimental to its host but under the influence of certain external factors not yet completely understood, such as trauma, fatigue, diet, and exposure, the disease becomes manifested. This theory has not yet been proved.

Because gouty individuals so frequently have abnormally high blood uric acid concentration and abnormal urinary excretion of uric acid, the disease is considered to be dependent upon an error in purine metabolism. The exact metabolic fault is not known, however, nor is the true significance of the hyperuricemia understood. Although other diseases may cause high blood uric acid values, the occurrence of hyperuricemia in children and close relatives of gouty individuals, in the absence of renal insufficiency and liver disease, logically appears to indicate the existence of the metabolic abnormality responsible for, or characteristic of gout. Further study of the blood uric acid content in relatives of gouty patients will undoubtedly clarify this, and by such a study the relationship of the metabolic fault to the clinical manifestations of gout may become evident, as will the mode of transference of this apparent inborn error of metabolism. We shall watch with great interest the course of events in the sons, D. and R., of Family II of this report. If in later years they show clinical evidence of gout, it will be apparent that the present hyperuricemia indicates the existence of the metabolic fault prior to gouty attacks. Further, should they or others with high blood uric acid values but without clinical manifestations of gout have children with hyperuricemia and gouty attacks, Garrod's theory of transmission of a " susceptibility " to gout would have scientific support.

This study indicates the importance of investigating the relatives of gouty patients for the presence of gout. By such an investigation in Family I of this report the existence of gout was established *for the first time* in the father and two brothers of the original patient (H). If, whenever the diagnosis of gout is made, all close relatives of the patient are carefully studied, many persons might be found to have gout at a much earlier time than would be the case in the ordinary course of events, and proper management of such individuals would eliminate much unnecessary suffering and incapacitation.

The findings in the families, herein reported, suggest that there is an important hereditary factor in the etiology of gout. We believe that the hereditary aspects of this disease have not been sufficiently recognized. However, whether or not *all* cases of gout are truly hereditary, or whether

the disease may be acquired, requires much further study. Further, the exact mode of transmission of an hereditary factor cannot now be stated, primarily because too few families have been carefully investigated. It is our hope that this report will stimulate further studies of similar nature so that the exact importance of heredity in relation to this disease might be understood.

SUMMARY

The families of two gouty individuals have been systematically studied. Each member was questioned and examined for evidence of gout; in most cases blood was quantitatively analyzed for uric acid, and in some instances joints were studied roentgenographically. Seven of the eight adult male members of these two families have hyperuricemia and five have clinical gout. In one family the father and all three sons have gout; in the other family a gouty father has two sons who have definite hyperuricemia but no other manifestation of gout. None of the females in these two families have any evidence of this disease. Case histories of the five men with gout are presented.

This study indicates the importance of investigating relatives of gouty patients for the presence of this disease. Some of the problems of the hereditary nature of gout are discussed.

BIBLIOGRAPHY

1. SCUDAMORE, C.: A treatise on the nature and cure of gout and rheumatism, 1819, Edward Earle, Philadelphia.
2. GARROD, A. E.: The inborn factors in disease, 1931, Oxford Press, New York.
3. GARROD, A. B.: The nature and treatment of gout and rheumatic gout, 1859, Walton and Maberly, London.
4. ALLBUTT, T. C.: Gout, in The Oxford Medicine, 1936, IV, pt. 1, chap. IV, 82, Oxford University Press, New York.
5. WEIL, M. P.: L'hérédité des goutteux, Presse méd., 1934, xlii, 701–702.
6. PRATT, J. H.: Gout, in Nelson Loose-Leaf Med., 1923, III, chap. 3, 37, Thomas Nelson and Sons, New York.
7. FOLIN, O., and LYMAN, H.: On the influence of phenylquinolin carbonic acid (atophan) on uric acid elimination, Jr. Pharmacol. and Exper. Therap., 1913, iv, 539–546.
8. FOLIN, O., and DENIS, W.: The diagnostic value of uric acid determination in blood, Arch. Int. Med., 1915, xvi, 33–37.
9. JACOBSON, B. M.: Uric acid in serum of gouty and non-gouty individuals: its determination by Folin's recent method and its significance in diagnosis of gout, ANN. INT. MED., 1938, xi, 1277–1295.
10. FOLIN, O.: Standardized methods for determination of uric acid in unlaked blood and in urine, Jr. Biol. Chem., 1933, ci, 111–125.
11. DE GALANTHA, E.: Technic for preservation and microscopic demonstration of nodules in gout, Am. Jr. Clin. Path., 1935, v, 165–166.
12. LOCKIE, L. M., and HUBBARD, R. S.: Gout: changes in symptoms and purine metabolism produced by high fat diets in 4 gouty patients, Jr. Am. Med. Assoc., 1935, civ, 2072–2075.
13. BAUR, E., FISCHER, E., and LENZ, F.: Human Heredity, translated by Eden and Ceder Paul from the Third German edition, 1931, The Macmillan Company, New York.

CHEMOTHERAPY OF PNEUMONIAS AND IMMUNITY REACTIONS *

By Jesse G. M. Bullowa, M.D., F.A.C.P., Nathan H. Shackman, M.D., and Daniel Stats, M.D., *New York City*

In the selection and application of our available resources for the treatment of pneumonias, we should be guided by consideration of the interaction of pneumococci and patients and the effect of our remedies on both. Final judgment must be based on clinical experience with adequately sized similar groups of patients treated with various therapies. Patients who completely recover from pneumonia without benefit of specific therapies do so by reason of their immunity response which completely destroys the invading bacteria; and such patients as a rule exhibit acquired immunity to the invading organism. Accordingly, the capacity to overcome infection, which is a cardinal characteristic of patients, must be considered when we compare the effect of different treatments.

The Effects of Therapies. Chemotherapy with sulfonamides, specific serum therapy, or a combination of both, are current methods of successful treatment. Serum therapy passively augments the specific immunity response. The effect of chemotherapy on the pneumococci and on the development of immunity deserves attention.

Therapeutically, the sulfonamides affect the pneumococci by killing them or depressing their vitality so that they produce less capsular carbohydrate. The capsular carbohydrate is that portion of the pneumococcus which gives pneumococci their specific character and their virulence or capacity to produce disease. In figure 1 (the graph) which is from work done in our laboratory with a standardized strain of pneumococcus III observed for growth with and without exposure to 5 mg. per cent sulfapyridine, it may be seen that the effect of the drug was not immediately noticed and the decrease in colonies did not occur until four hours had elapsed. After 26 hours the organisms escaped from the effect of sulfapyridine and the colonies increased in number. Much more carbohydrate was present in the control culture than in the one exposed to sulfapyridine. If a sufficient amount of an effective drug is in contact with the pneumococci for a sufficient time, all of them are killed (bactericidal action). All the organisms do not die at the

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Constance Lebair assisted in the statistical analysis.

same time and if the concentration is insufficient or the pneumococci are too numerous and resistant, only some are killed and the others are temporarily held in check (bacteriostatic action). After medication is discontinued these dormant organisms may become active again unless sufficient antibodies develop or are supplied.

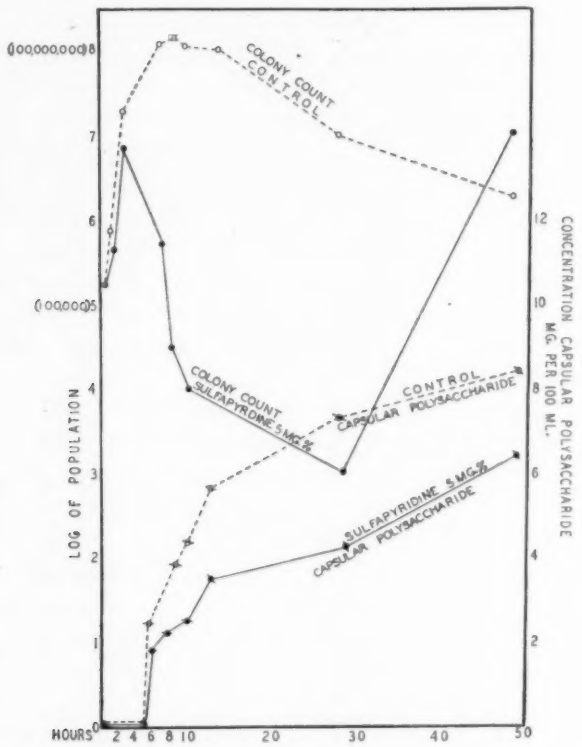


FIG. 1. Curves of growth and production of capsular polysaccharide with and without sulfapyridine. Pneumococcus III. In the presence of 5 mg. per cent sulfapyridine growth was unaffected for four hours. After the fourth hour there were fewer organisms than in the control. The number of organisms diminished until the twenty-sixth hour when their multiplication was accelerated so that at the forty-eighth hour there were even more organisms in the culture with sulfapyridine than in the control. The production of capsular substance in the presence of sulfapyridine was less than in the control.

The patient (figure 2) whose chart is shown was treated with sulfadiazine and a concentration was obtained sufficient to sterilize the blood and lower the temperature and permit development of antibodies. Only a very small amount of antibody was detectable for a single day. All the organisms were not destroyed—there was a reinvasion of the blood with a fatal outcome.

The Selection and Administration. The most effective sulfonamide drug is one which acts upon the organism causing the illness, penetrates the

tissues, and maintains a high concentration of free drug with little toxic action. It should be administered early in the disease while the organisms are few in number; the initial dose should be large so as to achieve promptly a high concentration; and further doses should be repeated sufficiently often to maintain the desirable concentration uninterruptedly for the shortest necessary period. The organisms are then all destroyed or so weakened that they do not overwhelm the immunity mechanism and there is less likelihood of toxic action which depends, in part, upon the amount of drug given.

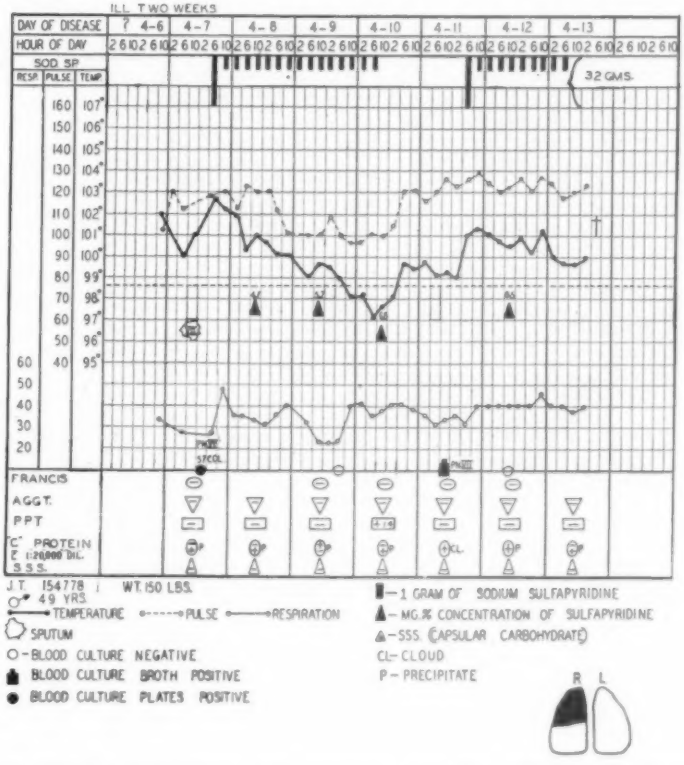


FIG. 2. 49-year-old man whose pneumococcus VII bacteremia was temporarily controlled with sulfapyridine. The chemotherapy was discontinued when the temperature was 97° F. Acute phase protein was present and on a single day there was a very small amount of precipitin. The organisms had not been completely destroyed by the drug or by the immunity mechanism.

A male patient (figure 3), 36 years old, was treated with sulfapyridine on the second day of his illness for a pneumococcus IV pneumonia of his left lower lobe. A high concentration was found, a total of only 18 grams of the drug was used and, on the tenth day, agglutinins were demonstrable. It will be noted that the drug was effective in the concentration obtained and the immunity mechanism was activated.

The absolute effectiveness of a sulfonamide drug upon pneumococci

varies from strain to strain.[1] Resistance of fastness of the pneumococci to the drug may be observed to develop in the ill patient, or strains of pneumococci preserved from patients treated with sulfonamides may be observed to have retained this resistance. Absolute effectiveness may be diminished by the poor concentration usually obtained in patients, or by poor tissue penetration, greater acetylation, greater toxicity or less amplitude of application. For instance, sulfadiazine is a very useful drug because it has a broad band of usefulness, being effective against staphylococci and *Bacillus Friedländer B.*, though in equivalent concentrations it is less effective than sulfathiazole or sulfapyridine against pneumococci.

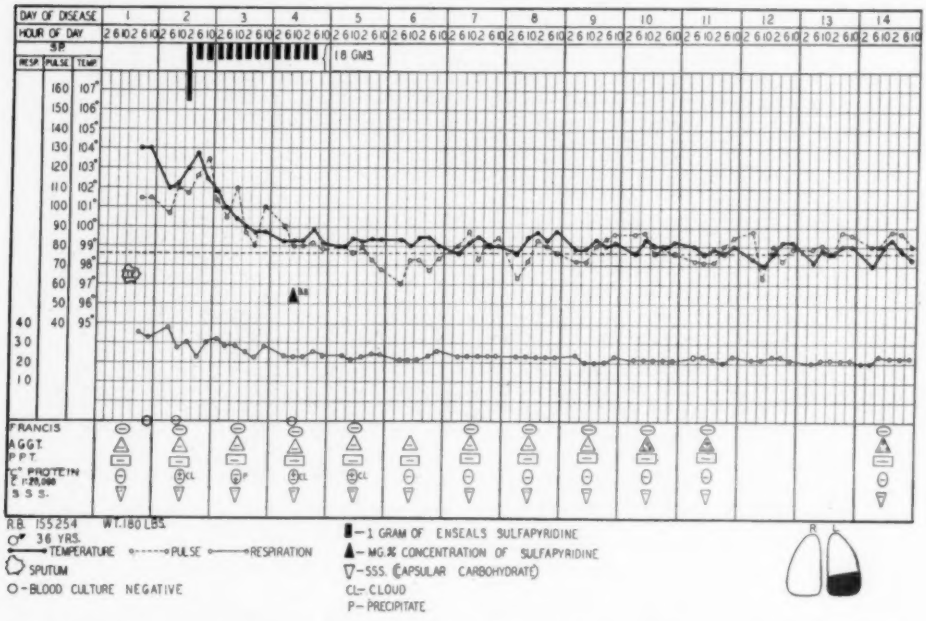


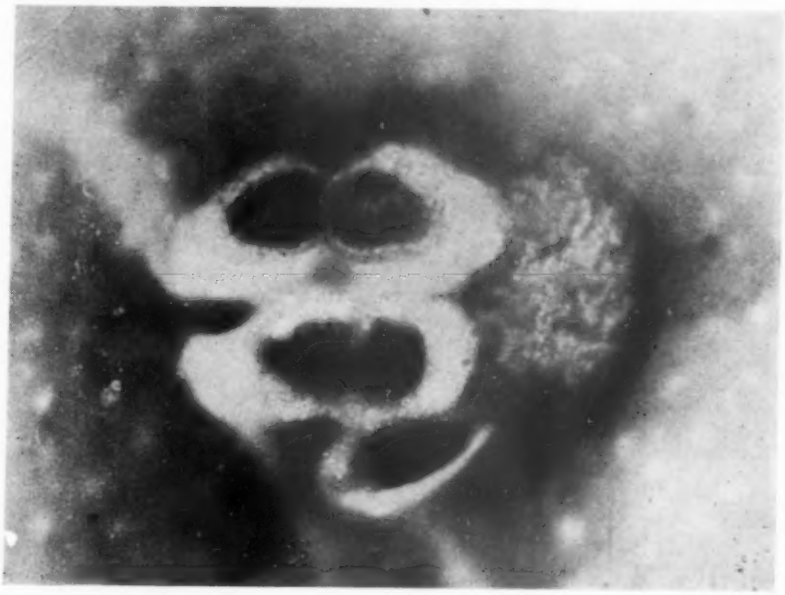
FIG. 3. The immunity developed in this patient on the tenth day—acute phase protein was absent on the sixth day. Only 18 gm. of sulfapyridine were used. Enteric coating of the sulfapyridine did not prevent nausea and vomiting.

Immunity. Immunity induced by pneumococci may be cellular or humoral as well as local and general (figure 4). The local cellular response is a multiplication of cells, dilatation of capillaries, migration of red blood cells, leukocytes and macrophages.

Leukocytosis and Leukopenia. Usually in response to pneumococcic infection there is a granulocytic leukocytosis which disappears when immunity develops either spontaneously or in response to therapy. When sulfonamide drugs are given the fall of the white blood count occurs with fall of pulse and temperature, as a result of the effective action of the drug. However, when the sulfonamide drugs are given for a long time, or to sus-

ceptible individuals, the migration of white blood cells may be depressed and an agranulocytic leukopenia may develop. Furthermore, leukopenia in which the per cent of granulocytes is not depressed may occur, due to the toxic action of pneumococci. In this last type of case the administration of sulfonamide drugs does not depress the count but causes it to rise. In these patients, though the white blood count is low, the bone marrow is active. When there is an agranulocytic leukopenia due to disease or other phenol-

RESPONSES TO PNEUMOCOCCI



Cellular		Humoral	
Local	General	Type Specific	Generic
Capillary Dilatation	Neutrophile Leukocytosis	Capsule Swelling	Acute Phase or "C" Protein
Tissue Cells Increase		Agglutinins	Nucleoprotein
Migration of: Red Blood Cells		Precipitins	Antibody
Leukocytes		Dermal Response (Francis)	
Macrophages		Sputum Response (Frisch)	
		Phagocytosis	
		Bacteriolysis	

FIG. 4. Electron-microscopic photograph of pneumococci.

containing drugs, an additional insult to the bone marrow with sulfonamides may be hazardous. The migration of leukocytes into infected cavities may be halted by the sulfonamides so that empyema pus fails to thicken and purulent infiltration of the meninges is lessened. The density of consolidation may be less. This chemotactic depression or counter action of leukocyte migration may prove advantageous.

Complement. Whether recovery from pneumonia requires active complement to be present is still unknown, but if it is required it would be

desirable to determine whether complement activity is impaired by sulfonamide administration. The hemolytic complement was studied in a human system and found unaffected in normal persons and in pneumonia patients to whom sulfonamide drugs had been administered in the usual way.

Capsular carbohydrate induces the production of type specific antibodies. These antibodies precipitate capsular carbohydrate (thereby limiting edema in the lungs), and swell the capsules of pneumococci and agglutinate them, and at the time of crisis, by sensitizing them, assist in both lysis and phagocytosis. These processes may be observed in the sputum, as pointed out by Frisch.[2] The carbohydrate produces little if any harm in the absence of pneumococci which otherwise consist largely of nucleoprotein. We have observed carbohydrate continuously present for months in the blood of a patient with spondylitis due to pneumococcus III.

To a degree, the virulence of a pneumococcus is determined by the amount and character of the *capsular carbohydrate* produced and its ability with pneumococci to act as an antigen or induce the production of antibodies. In some cases the carbohydrate is detected in the blood and in the urine or in an infected serous cavity. The significance of detecting capsular carbohydrate in the blood was investigated. The patients were being rotated for treatment with serum therapy, chemotherapy and the combination. These studies covered two periods. In the first period, from November 20, 1939 until February 18, 1940 the study was confined to infections with pneumococci of types I, II, III, IV, V, VII and VIII. The results have already been reported.[3] Another series was studied from July 1, 1940 to May 1, 1941. The series differ because the latter study was made over a longer time including periods of lesser virulence of pneumonia and the cases were studied much less intensively than the earlier cases. Capsular carbohydrate was detected in the blood of 6.6 per cent of the combined groups (see figure 5). It was not found in the blood of 97 type I patients, 51 type IV patients or 16 type V patients. It occurred most frequently in type III patients with an incidence of 13.5 per cent of patients. In the first series it had been present in 27.5 per cent of the pneumococcus III patients. It was found in three of the 33 type II, in five of the 101 type VII, and in six of the 65 type VIII patients. The death rate in the patients with detectable capsular carbohydrate was 58.1 per cent (18 deaths among 31 patients). It was only 12 per cent in the cases without carbohydrate, 53 among 458 patients. When there was neither bacteremia nor capsular carbohydrate present (figure 6) our death rate, regardless of kind of treatment, was 7.5 per cent and when there was a bacteremia present without any capsular carbohydrate the death rate was 35 per cent. The death rate in patients who had capsular carbohydrate without bacteremia was 60 per cent, and with both bacteremia and capsular carbohydrate 56.2 per cent. The detectable specific carbohydrate occurred about five times more frequently in patients over 40 years of age than in those younger and twice as frequently after the fourth day of disease than in those coming for treatment earlier.

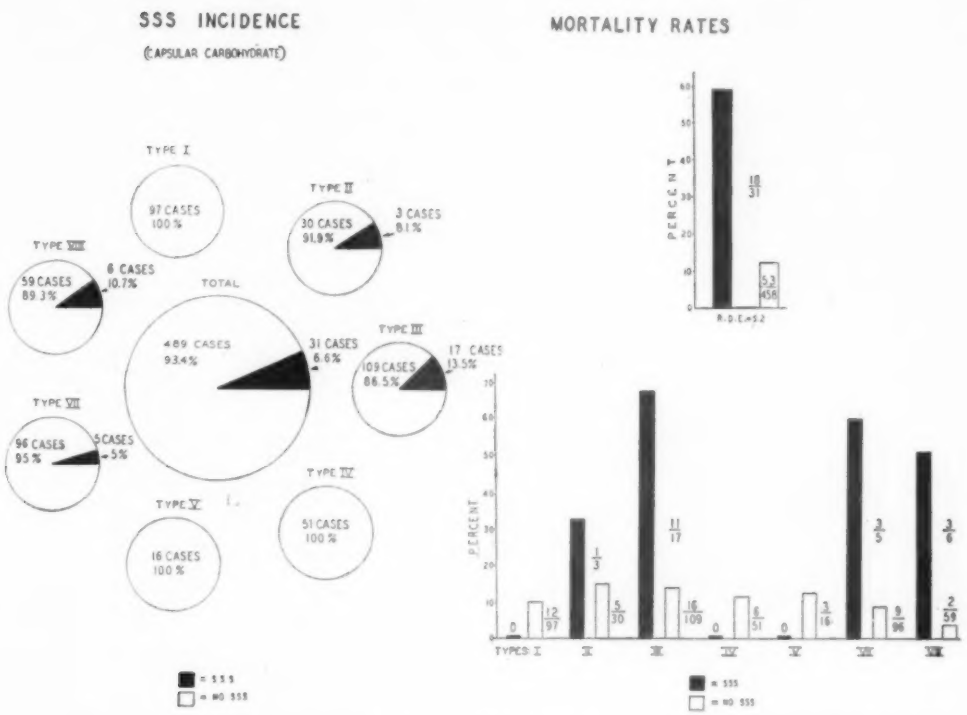


FIG. 5. Pneumococcic I, II, III, IV, V, VII, VIII pneumonias, Nov. 20, 1939–Feb. 18, 1940 and July 1, 1940–May 1, 1941. Capsular carbohydrate (SSS) incidence in two series of pneumococcic pneumonias combined and by types and the influence of its detectable presence on mortality combined and by types.

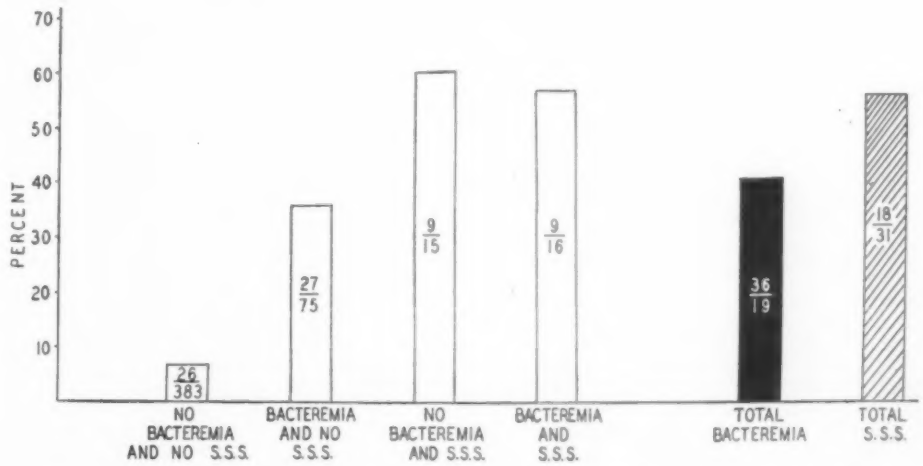


FIG. 6. Mortality rates of Pn. I, II, III, IV, V, VII, VIII pneumonias in relation to detectability of SSS and bacteremia, Nov. 5, 1939–Feb. 18, 1940 and July 1, 1940–May 1, 1941.

Specific antibodies (agglutinins and precipitins) appeared in 66 per cent of the 88 patients treated with chemotherapy of the types included in the analyses (figure 7). Antibodies developed least frequently in the pneumococcus III patients and most frequently in those infected with pneumococcus VII. Almost two-thirds of the pneumococcus I, three-fourths of the pneumococcus II, one-half of the pneumococcus III, two-thirds of the pneumococcus IV, 57 per cent of the pneumococcus V and 70 per cent of pneumococcus VIII patients developed antibodies. Antibodies were more frequently detected in patients under 40 years of age than in those above 40, i.e., in 72.5

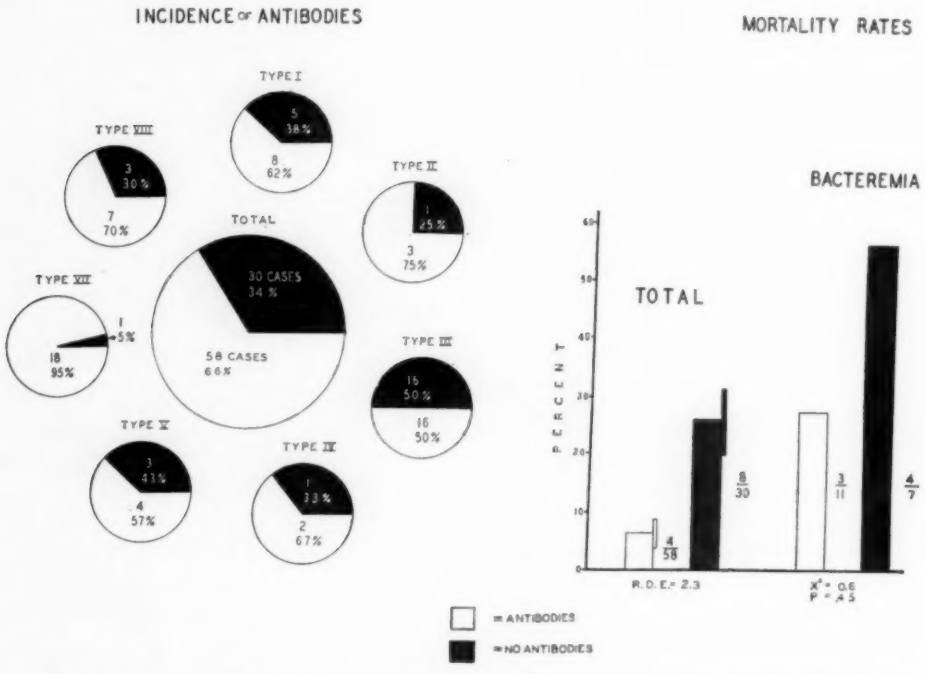


FIG. 7. Pneumococcic I, II, III, IV, V, VII, VIII, pneumonias—chemotherapy. Nov. 20, 1939–Feb. 18, 1940 and July 1, 1940–May 1, 1941. Incidence of antibody development in certain pneumococcic pneumonias given chemotherapy, and the influence of the presence of antibody on mortality in all the patients and also in those with bacteremia.

per cent of those under 40 and 60 per cent of those over 40. In the older patients there was a higher mortality rate; the patients who did not develop antibodies had a mortality almost four times greater than those who did develop them. The death rate in the patients who developed antibodies under 40 years of age was 3.5 per cent. Those who did not develop antibodies in that age group had a death rate of 9.1 per cent. In those over 40 the death rate was 10.3 per cent when antibodies appeared, and when they were absent it was 36.9 per cent. Of the cases treated early, only one of the 22 who developed antibodies died (5 per cent). Three of the 36 patients

treated after the fourth day who developed antibodies died (8.3 per cent). Eighty per cent of 58 patients, in whom the exact time of onset was known and who received chemotherapy, did not develop antibodies until after the eighth day. None of the patients who developed immunity before the eighth day died. The importance of immunity development was exemplified in a 29-year-old pneumococcus III patient (figure 8) who was treated with sulfadiazine on the seventh day of his illness. On admission and until the

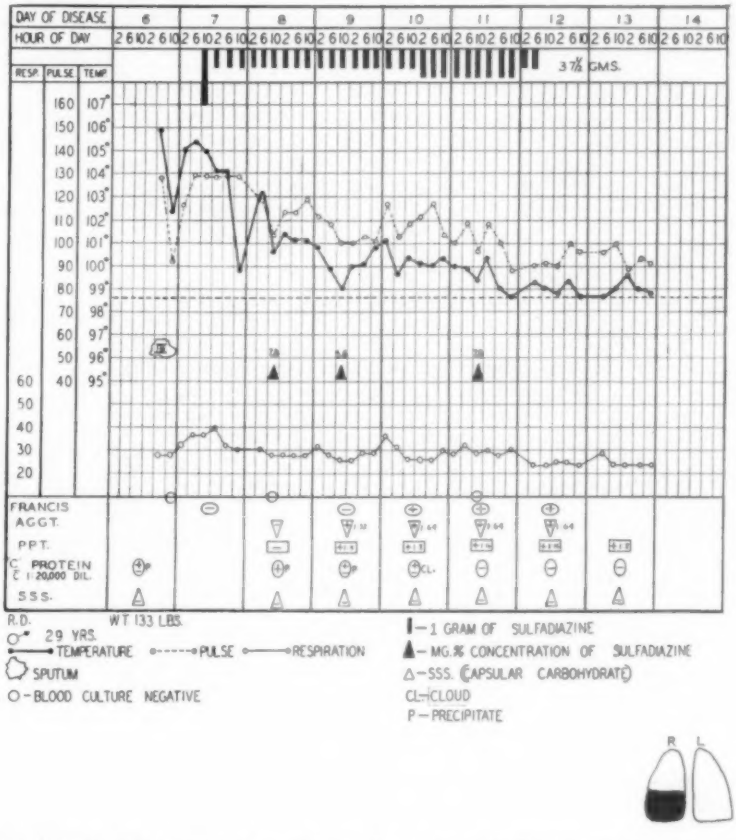


FIG. 8. A 29-year-old man who was treated with sulfadiazine on the seventh day developed immunity on the ninth day. Treatment was continued until the twelfth day. This was probably longer than necessary. There was no reason to continue the drug longer.

ninth day there was no evidence of protective immunity. On this day his temperature was normal but the pulse was accelerated. On the ninth day also there was a faint immunity response. This increased on the tenth day and the Francis test became positive as well. Because the drug concentration had been low and the temperature and pulse were elevated, increased dosage was given. There was firm immunity, "C" protein disappeared on the eleventh day, and the drug was stopped.

A separate analysis of 12 pneumonia patients (figure 9) treated with sulfapyridine or sulfadiazine revealed that the skin test with type-specific polysaccharide became positive in 25 per cent of the cases on the sixth to tenth day of the disease without relation to temperature fall. Two of these three patients also developed agglutinins and precipitins in their blood. Only one patient in the group died. He failed to develop a positive skin test; precipitins were faintly demonstrable on only one occasion. The drug was prematurely discontinued (figure 2). Of the eight recovered patients who failed to develop a positive dermal reaction, four developed precipitins as well as agglutinins and one developed precipitins only.

Acute Phase Protein ('C' Protein). In addition to the specific carbohydrate which is in the capsule of the pneumococcus and which stimulates the production of specific antibodies, there may be extracted from the bodies

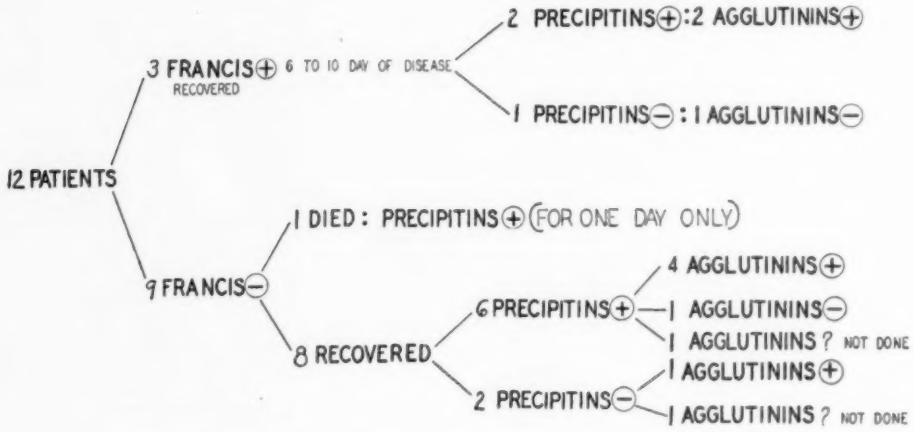


FIG. 9. Immunity response to chemotherapy.

of decapsulated and no longer type-specific pneumococci, another carbohydrate which is not type specific—the 'C' substance.* During the acute phase of illness, before specific immunity has developed, 'C' substance precipitates 'C' protein from the serum of patients suffering from pneumococcal, streptococcal, staphylococcal, *Bacillus Friedländer* infections, and alsc from infections due to some other agents. This substance is evidence of the presence of a bacterial irritant, because when it continues to be present the infection persists. It is not present in the mild bacterial infections or in those febrile conditions due to organisms which usually do not produce pneumonia. When 'C' substance fails to appear in pneumococcic pneumonia

*'C' substance for these tests was generously supplied by Dr. Walther Goebel of the Rockefeller Institute Hospital. The test was performed by adding 0.2 c.c. 'C' substance, 1: 10,000 to 0.2 c.c. of serum centrifuging 20 minutes at 2000 R.P.M. and reading in a strong light with controls of saline and serums which have been negative. A faint but doubtful cloud with 10 gamma of 'C' substance in 0.4 c.c. of the serum and 'C' substance mixture was considered negative.

it may signify failure of response. It was not present in five very young children who died, two of whom showed demonstrable specific carbohydrate in the blood. In 417 adult pneumonia patients only 27 or 6.8 per cent failed to show it (figure 10). It was found in 89.5 per cent of cases treated or coming in before the fifth day. In those treated or coming in later, it was present in 96.1 per cent. Some of the patients did not have 'C' protein on the first examination but had it subsequently. In the patients coming in before the fifth day it appeared or was present on the second or third day. In 90 per cent of the patients showing it, it was present by the ninth day of disease. Twenty-eight were not examined for 'C' protein on discharge and

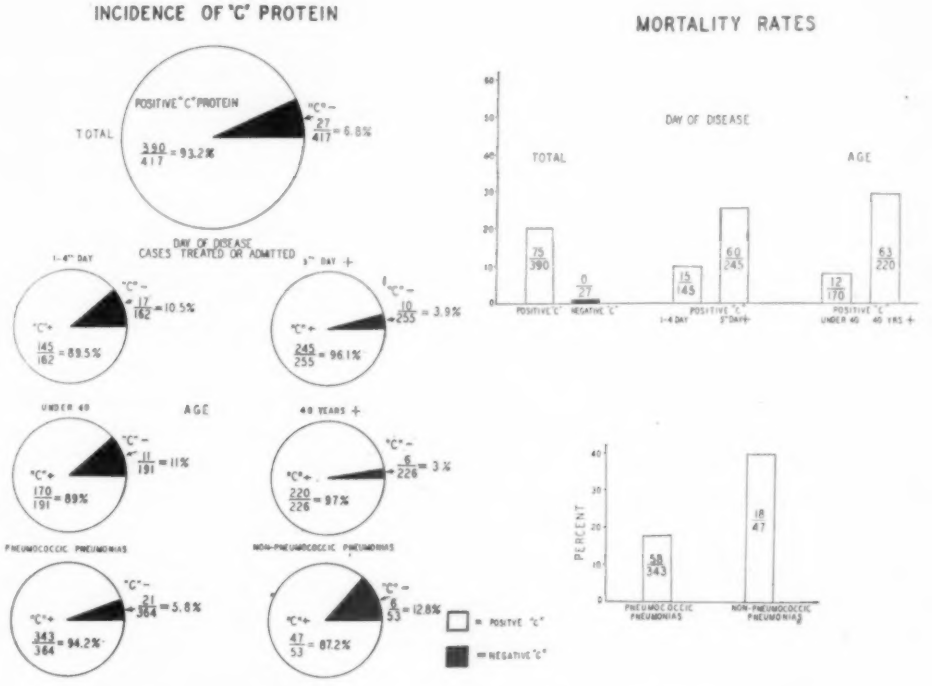


FIG. 10. "C" protein adult pneumonias. Nov. 5, 1940–April 5, 1941.

eight were discharged with 'C' still in the blood. It disappeared in over half the cases by the tenth day of disease. It was more frequently found in patients over 40 years (97 per cent) and in proved pneumococcic infections, 94.2 per cent. Among those patients who had 'C' protein the older patients, those treated late in the disease and those with non-pneumococcic pneumonias, showed the highest mortality (figure 10). There were no deaths among the 27 negative 'C' protein cases. In 15 per cent of cases the 'C' protein disappeared before the temperature fell. In the remaining 85 per cent of cases the 'C' protein disappeared within three days after the temperature fell. There were 23 patients who recovered when 'C' protein persisted

beyond three days; in 16 cases the pneumonia had not resolved, as shown by persisting signs; in one a bronchiectasis was suspected; serum sickness was present in five cases and pleural effusion in two cases. Of those who died when 'C' protein was present, i.e., 75 cases, 27 were patients who lived less than 24 hours after admission or after treatment was started. The other 48 deaths were in patients who had had more than one 'C' determination. In 13 of these the cause of death was a condition associated with the pneumococcic infection. Such conditions were pneumococcic meningitis in four cases, empyema in two instances, pericarditis in two cases (one having endocarditis as well), lung abscess in one, pleural effusion in one, and pulmonary edema in three. In nine of the patients who died therapy had failed because it was started late; in only one had it been commenced before the fifth day. In five more cases therapy failed because concentration of the drug was insufficient. There may have been unrecognized purulent conditions. In the other 21 cases death was due to an associated disease, 2 to pulmonary tuberculosis, 15 to cardiovascular renal disease (1 of whom died in collapse, 1 an excessively obese patient, 11 in cardiac failure, 1 with cerebral hemorrhage, 1 with azotemia). Other causes of death were diabetic coma (1), carcinoma of the esophagus (1), subphrenic abscess (1), rheumatic heart disease (1).

The study of 'C' protein response may be of value in diagnosis and in treatment when correctly interpreted. Its presence in large amount indicates response to an irritant and its disappearance after chemotherapy may indicate that a febrile episode is not due to continued infection or complication but possibly to the chemotherapeutic agent.

Causes of Failure with Chemotherapy. When sulfonamide drugs given in the usual dose are ineffective in reducing the pulse and temperature of patients with pneumonia it is important to search for the explanation (table 1). The following should be thought of as possible explanations:

(1) The diagnosis may be incorrect in that the consolidation may be due to organisms not affected by sulfonamides.

(2) The concentration of the drug may be one that is ineffective. A low concentration may be due to insufficient dosage, poor absorption, excessive acetylation, or poor tissue penetration.

(3) There may be too many organisms because the disease is treated late and the organisms are either not killed or are attenuated too slowly with the amount of drug present.

(4) The pneumococci may have become fast. This is not frequent, but it does occur, and much higher concentrations of the drugs than usually employed may be required. Sometimes the organisms when grown in culture are killed by sulfapyridine, but in the presence of serum or exudates the drug is in part or completely inactivated by anti-sulfonamide substances. Unless very high concentrations are employed in such cases the drug fails as a therapeutic agent.

(5) When pneumococci are in pus collections, both the large number of organisms and the anti-sulfonamide substances may make chemotherapy ineffective whether the drug is administered either orally or parenterally. Sometimes in these purulent collections capsular carbohydrate and living organisms are present though absent from the circulating blood. As a rule, the immunity response and protection become exhausted unless surgical drainage is promptly employed. Evacuation, lavage and local application of sulfonamide drugs in very heavy concentrations have been proposed and used successfully.

(6) There may be severe toxic phenomena affecting the nervous system, the liver, the bone marrow and the kidneys or collapse may have been induced by the drugs.

(7) Finally, there may be, in certain patients, a failure of the immunity responses as already outlined so that the organisms that have not been killed may again become active. For the detection of such patients typing and studies of the immunity mechanism are necessary. Accurate data may make it possible to save the patient.

TABLE I

Causes of Failure of Chemotherapy

1. Wrong diagnosis
   Pneumonia not due to sulfonamide affected organisms.
2. Ineffective concentration due to non-absorption, conversion, rapid excretion or insufficient penetration.
3. Too many organisms; late
4. Fastness—original or developed
5. Antisulfonamide substances; pus
6. Toxic action
7. Failure of immunity response

SUMMARY

The responses of the body to invasion of the pneumococcus have been presented, and it has been shown that there are immunity responses which contribute to recovery when sulfonamides are used. If treated very early in the disease, the pneumococci are attenuated or killed by these drugs. Immunity is established at the usual time as if the patient had had a mild infection and had recovered spontaneously. Although in most young patients other than infants, treated early, chemotherapy is sufficient completely to suppress the disease agent or to render it relatively innocuous, there are patients, those most severely stricken, who may require assistance; to them antibodies must be supplied to augment the immunity response. Moreover, when pneumococci resist chemotherapy because they are fast, they may respond to type specific serum therapy, and on this account specific typing and immunity study of blood and sputum are necessary for the best care of patients. When non-specific (for type) chemotherapy is employed patients who develop specific antibodies require neither serum therapy nor additional chemotherapy.

For such patients tapering off the drug is unnecessary and may be harmful. In addition to specific immunity, the diagnostic importance of the presence of acute phase or ' C ' protein is discussed.

REFERENCES

1. Osgood, E. E., Bullowa, Jesse G. M., Bukantz, S. C., and Brownlee, Inez: The effect of sulfapyridine alone and with serum on pneumococcic pneumonia and pneumococcus infected marrow cultures, Am. Jr. Med. Sci., 1940 cxcix, 364–380.
2. Frisch, Arthur W.: Sputum studies in pneumonia as an aid in prognosis, Am. Jr. Clin. Path., 1940, x, 417.
3. Bullowa, J. G. M., deGara, Paul F., and Bukantz, Samuel C.: Type specific antibodies in the blood of patients with pneumococcal pneumonia: detection, incidence, prognostic significance and relation to therapies, Arch. Int. Med., January, 1942.
4. Bukantz, S. C., deGara, Paul F., and Bullowa, J. G. M.: Capsular polysaccharide in the blood of patients with pneumococcal pneumonia: detection, incidence, prognostic significance and relation to therapies. To be published in Arch. Int. Med.

PROTEIN DERIVATIVES AS FACTORS IN ALLERGY *

By Robert A. Cooke, M.D., F.A.C.P., *New York, N. Y.*

Nutritional or deficiency disturbances are seen in persons exhibiting manifestations that are allergic or are attributed to allergy. Occasionally, and especially in young children, genuine sensitizations to many common foods interfere with a sufficient and balanced diet and malnutrition results; but more frequently such disturbances arise from dietary restrictions imposed by the physician, based upon improper interpretation of or undue reliance on skin tests or to the acceptance without adequate proof of a patient's own story of food idiosyncrasies.

As my contribution to this Symposium on Metabolic Diseases, however, I am not going to dwell upon these aspects, but because of their present importance in the theory and practice of allergy I have chosen to consider the relation to allergy of certain metabolic derivatives of protein; namely, histamine, an end product capable of direct toxic effects; proteose, an early product of protein digestion which has antigenic capacity and acts only through the medium of antibody; and, very briefly, nucleic acid.

Histamine

From the beginning of the studies in anaphylaxis by Richet, Theobold Smith, Otto and others, search was made for a hypothetical toxin, so-called anaphylatoxin, responsible for the characteristic symptoms of shock.

In the Herter Lectures delivered at the Johns Hopkins University in 1919, Dale [1] reviewed the discovery and the early studies on histamine by himself and his associates. On account of its physiological action, its potency and its presence in normal tissues, "the suggestion," as Dale says, "lay near at hand that the long-sought active substance was 'histamine,' and that the production of the latter in the system was the cause of the anaphylactic shock." These workers had demonstrated that histamine produced a contraction of smooth muscle fiber, it depressed capillary tone and rendered capillary walls permeable. In other words, when injected into animals it appeared to reproduce through the effects mentioned some of the more essential phenomena of anaphylactic shock. It was later shown that when injected intradermally it promptly created a typical allergic type of wheal. These findings revived an interest in anaphylactic studies but nothing much was accomplished until a method for the quantitative analysis of histamine was devised by Barsoum and Gaddum [2] in 1935, later modified by Code [3] in 1937. The method, however, is not a direct estimation of the

* Read at the Boston meeting of the American College of Physicians, April 23, 1941.
From the Department of Allergy, The Roosevelt Hospital, New York City.

organic base in fluids and tissues but a biological assay using smooth muscle contractility as the indicator. Such assays always give grounds for objection. In this particular instance substances other than histamine may be present which stimulate smooth muscle contraction, so that analyses are suggestive rather than conclusive.

On theoretical grounds the establishment of the fact that histamine is the active factor or even one of the active factors in anaphylactic shock would be important not only of itself but also because it might give a new basis for studies in certain allergic reactions of man. Space does not permit a critical review of recent experimental work in anaphylaxis. Suffice it to say that one is definitely impressed with the fact that many, perhaps most, workers believe that histamine is an essential, if not the factor in experimental shock. For example, Dragstedt,[4] speaking of peptone reactions in dogs, says "We have been able to demonstrate that this reaction is accompanied by and due to the liberation of histamine just as is the case in anaphylactic shock."

While it seems likely that histamine is liberated in the shock, most workers have given little consideration to the possibility of other and perhaps even more important factors until the recent publication by Campbell and Nicoll.[5] They showed that rat uteri, "unaffected by ordinary doses of histamine, respond in the tissue bath to some substance released by sensitized guinea-pig lung tissue during anaphylactic shock." Evidently some substance other than histamine was liberated.

In some recent (still unpublished) studies in my laboratory with Drs. Wing and Stull we have come to a similar conclusion from a very elementary but different procedure similar to that of Schild.[6] The sensitized guinea-pig uterine horn was suspended in the tissue-bath in Tyrode's solution and repeatedly shocked with histamine until it failed to contract, histamine remaining in the bath. When the horn had relaxed, antigen was added and a prompt and maximum contraction occurred. This is illustrated in figure 1. Thus, to quote Schild with whom we agree, "it would appear . . . that either histamine released from the cell has a different action from that of histamine applied to the cell surface or it plays only a secondary part in anaphylactic shock." In experiments with atropinized muscle the results were the same, hence acetylcholine was not the factor.

In this connection, but without direct bearing on allergy, the important conclusions of Menkin[7] in his studies on inflammation should be mentioned. Lewis[8] has suggested that all capillary permeability in tissue injury was referable to a chemical H-substance, presumably histamine. Menkin's studies "indicate that the active factor recovered from an inflammatory exudate which is capable of inducing increased capillary filtration primarily by injury to the endothelial wall, does not seem to be histamine nor is it the H-substance in so far as its properties are supposed to resemble closely those of histamine." This substance finally isolated and crystallized by Menkin[9]

has been called leukotaxine. As a result of this work histamine is again deprived of its importance as the sole causative agent of increased capillary permeability.

I have discussed these various experimental studies because of their significance in the clinical studies with histamine that we shall now review. With regard to anaphylaxis, however, we must conclude that while histamine may be one factor, there are certainly others of equal or greater importance, the chemical nature of which is not yet known.

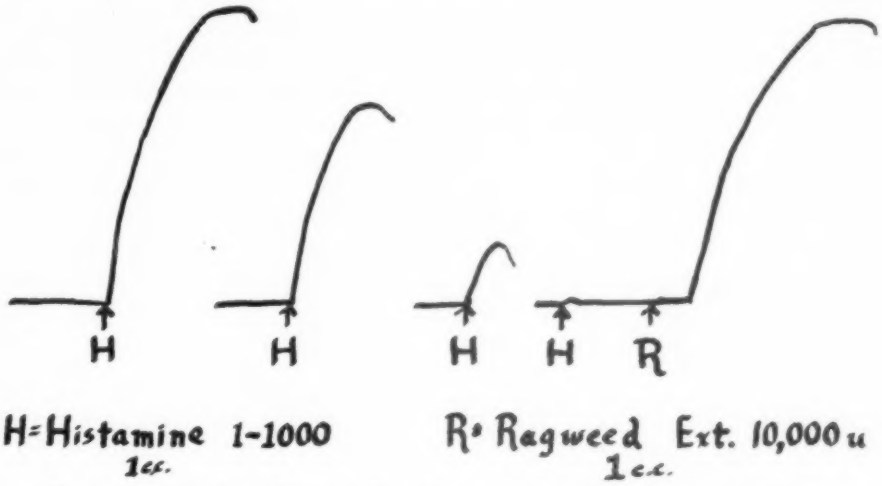


FIG. 1. Histamine-antigen reactions of ragweed sensitive guinea pig uterus.

Based upon the studies in anaphylaxis and because it produces an allergic type of wheal in the skin, histamine or H-substance, as Lewis [8] prefers to call it, is blamed by one or another investigator, definitely or by implication, for such clinical conditions as traumatic shock, serum shock, serum disease, angioedema, vasomotor rhinitis, asthma, eczema, various types of headache, Menière's disease, and the urticarias, including those due to physical agents.

Let us examine certain clinical aspects more fully. The statement is made that if a spontaneous urticarial wheal appears in a certain area it will not reappear in that area for 36 to 48 hours, the skin is unresponsive, due presumably to a failure of the cells to form the H-substance. Alexander [10, 11] has observed this in urticaria due to cold. I, myself, with a much more limited experience, have not been able to verify this, either for the spontaneous wheal or for that due to cold. In fact, in one of my patients with cold allergy the reapplication of ice to the wheal site made 24 hours previously led to a more rapid and greater wheal than the first application. In this same patient the right hand was immersed in ice water until edema was produced. Three hours later both hands were immersed in ice water. The edema that developed in the right hand was greater and more prompt than that of the left. Unresponsiveness was not demonstrated. Such exceptions to the rule are not adequately explained by the present theory, nevertheless

the so-called unresponsive phase has been made the basis for and, as Alexander says, "may well explain the successful treatment of chronic urticaria with daily injections of histamine . . . since histamine presumably provokes the production of H-substance." He further says that histamine injections were given "on the theory that H-substance would be released generally. The unresponsive phase was maintained by daily subcutaneous treatment," and "it was surprising to discover the degree of tolerance that could be established." This latter point of view is upheld by Farmer [12] and others.

The majority of writers on clinical effects of histamine fail to discuss its theory, content to rest their case on the clinical results of histamine therapy. The theory, however, is inconsequential—it is the fact, the result, that counts, and so far as I can observe, the results of histamine therapy are reported as quite uniformly successful. No definitely adverse reports have recently appeared.

With some reluctance, therefore, I feel impelled to record the experiences that I and my associates have had with histamine. They may be summarized as follows: (1) Normal non-allergic persons and allergic patients when skin tested with histamine solutions react alike. A slight positive intracutaneous reaction first develops with a dilution of 1–10,000,000 of histamine base, that is 10^7 with a range from 10^6 to 10^8. This means that there is no greater reactivity to histamine in the allergic than in the non-allergic group. This agrees with similar findings of Gotsch [13] and of Lass,[14] and contradicts the theory that allergic persons are more reactive to histamine than normal non-allergic persons.

(2) Using subcutaneous injections, beginning with 0.01 milligram of histamine base, we could increase the dose up to about 0.1 milligram, at which level a good general reaction with flushed face resulted in 90 per cent of the 20 allergics and of the 40 non-allergic normal controls. There was no difference between the two groups. But more significant still, no increase of tolerance was observed nor could it be obtained in either group by long continued injections once a definite but slight pharmacological effect was produced. Larger doses could be given but always with greater reaction.

(3) Therapeutic injections were given to 10 patients with urticaria over periods of 4 to 12 weeks and in no case did we observe any improvement. Daily injections were used the first week, beginning with very small doses and increasing up to the first sign of slight reaction, usually 0.1 milligram or slightly more of histamine base, which dose was then given every other day for at least a week, then twice a week, and finally once a week. Desensitization is the term applied to this treatment by some. This seems to me erroneous if used in its immunological sense, and since we are dealing with an immunological problem it should be used in this sense.

(4) Two years ago in my clinic, Hampton studied the blood of five patients taken during and after constitutional reactions induced during the course of pollen therapy and of two patients with severe giant urticaria.

Code's technic was used. In no case was there evidence of an increase of blood histamine during the allergic reaction.

In short then, with regard to clinical studies, my results are not in accord with most of those reported. I find no unresponsive phase in urticaria, no increase of tolerance to histamine, no clinical result in chronic urticaria, and no evidence that histamine is increased in the blood during general allergic reactions. I believe, therefore, a critical and even a skeptical point of view is still warranted, both as to the rôle of histamine in allergy and as to the therapeutic benefits to be derived through its use. Not that one objects to its general use, in fact we should favor it, for thus its true value or lack of value will the sooner be established, just as happened recently with that other widely heralded allergy remedy—histaminase.

Proteoses

The second protein derivative to be considered is proteose. The development of sensitization in animals to substances other than natural proteins has generally been regarded as impossible. Lipins, polysaccharides and simple chemicals are spoken of as antigens, but they stimulate antibody formation only when bound to protein and therefore are not antigens—generators of antibody—in the strict sense of the word, but are rather determinants of specificity, called "haptens" by Landsteiner,[15] with a capacity only for reacting with preformed antibody.

The digestion products of protein, such as proteose, have likewise been considered as non-antigenic and I find no evidence that they may behave as haptens. Fink [16] fully reviewed the work up to 1914 and concluded that any claims for antigenicity of proteoses were based on unsatisfactory evidence. Since then relatively little work has been done, but such as has been done by Zunz [17] and others is definitely unconvincing and the consensus, as expressed in the textbooks on immunology by Gay [18] and Zinsser [19] is that capacity for producing or reacting with antibody has been lost in the earliest stage of protein breakdown.

By a series of rather strange coincidences, I and some of my associates were led to reinvestigate the question of sensitization to primary and secondary proteoses. In brief, the story begins with the observation of a fairly severe allergic reaction, occurring promptly after the second injection of tetanus toxoid, in a patient in the Fall of 1938. Such reactions have been noted by Jones and Moss,[20] Hall,[21] Gold,[22] Parish and Oakley,[23] Whittingham,[24] and Cunningham.[25] Our studies [26] of this case showed that a sensitization had developed to the supposedly non-antigenic protein derivative, proteose, used in most tetanus culture media and present in the toxoid. This stimulated our interest in the anaphylactogenic possibilities in animals and experiments with the commercial peptones on guinea-pigs yielded positive Dale reactions in 18 of 19 trials.

Extended studies by some of my associates [27] with proteoses prepared

from known sources showed definite and new specificity in the experimental guinea-pig for a number of them, such as the primary proteose of milk whey and casein and the proteoses of beef and chicken. The question then arose as to the significance of such findings in certain of the food sensitivities of men. Since products in the early stages of digestion are antigenic, a means might be at hand to explain and to diagnose certain definite clinical reactions after the ingestion of foods that give negative skin tests when the original protein is tested. A correct and definite diagnosis of food sensitivity would be of value because today, among those interested in the field of allergy, there is a wide diversity of opinion as to the incidence of food sensitization. This difficulty is due in part to the fact that skin tests are often positive to a food that can be eaten with impunity and conversely, tests may be negative to foods that definitely cause clinical reactions. The former may be explained on the basis that skin reacting foods are altered by digestion and absorption and never reach the sensitized cells in sufficient amounts to set up a clinical reaction. The second observation, negative tests with clinically reacting foods, deserves further comment. The usual positive skin test with pollen extract in hay fever subjects is an immediate reaction. The clinical reaction following absorption of pollen from the air is likewise an immediate reaction. That the clinical reaction must follow immediately upon contact of an antigen with the sensitized cell seems to me a self-evident fact inherent in the immunological nature of such antigen-antibody-cell combinations. In the reactions to inhaled allergens, such as pollens, this is exactly what takes place. With the skin reacting and clinically reacting food allergens there may be an apparent delay of the symptoms up to perhaps one hour, due to the slower absorption through the gastrointestinal tract.

What then may be said regarding the allergies to ingested food that regularly develop several hours after the ingestion of a particular food which gave no skin reaction on test? At a meeting of the American College of Physicians in Boston in 1929, I presented a paper on "The Delayed Type of Allergic Reactions."[28] The clinical features of the four cases presented were: (1) that a food was the factor in all the cases; (2) following the ingestion, reaction was delayed up to 30 hours; (3) the reaction or incubation time was quite definitely fixed in each case; (4) the skin reaction to the original food was always negative before as well as after the clinical reaction. It was later suggested[29] that the real antigen in such cases might be a derivative of the food, something elaborated by the body from the food, and if this product were known and tested it might give a positive reaction. Now our story begins to link up with the observations on proteoses. Using solutions of primary and secondary proteoses prepared from known sources, we have tested a series of 39 allergic persons and found five that gave a positive skin test and positive passive transfer test but were negative to test with the original protein.

Let me present briefly the important features of one of the five cases studied. C. Z., male, 30, first seen in September 1938. He was admitted to the Roosevelt Hospital with severe status asthmaticus which began 25 days prior, following a respiratory infection. He was sensitive to ragweed.

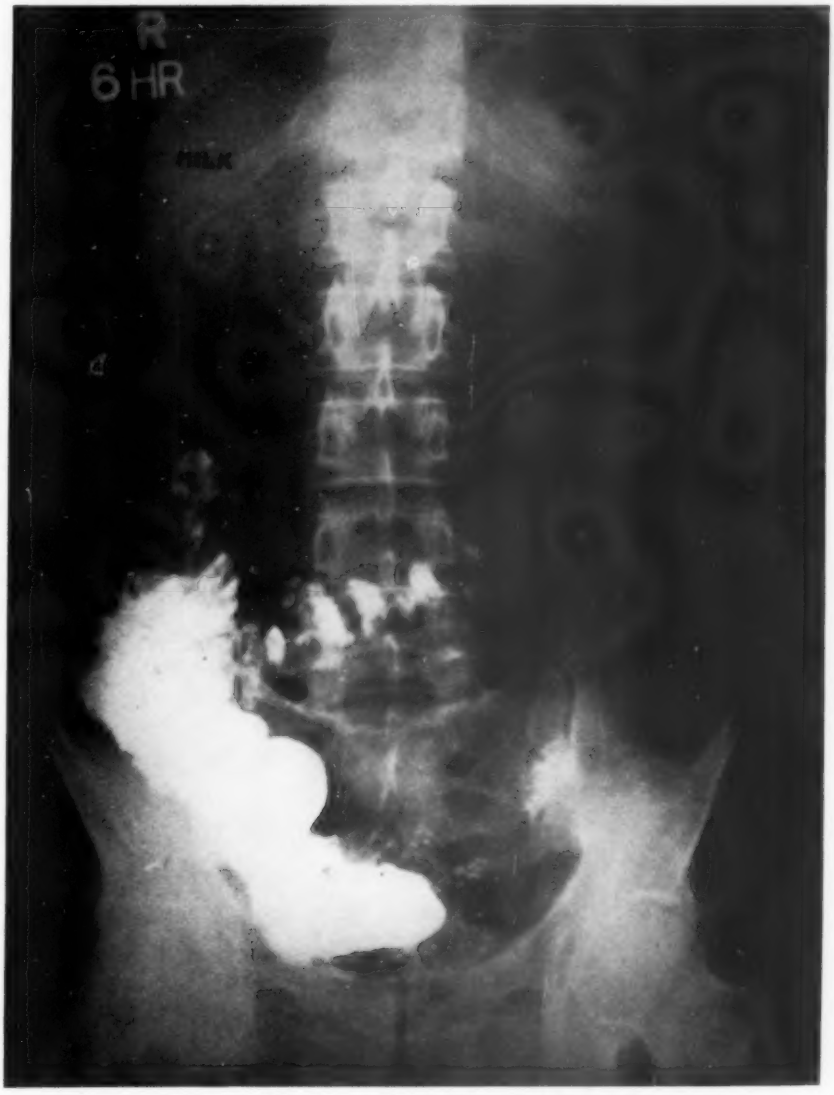


FIG. 2. Six hours after barium without milk.

Food tests were negative and there was no definite history of food idiosyncrasy or aversion, but the patient was suspicious that milk did not agree with him. He had also a chronic sinusitis involving the left antrum. In spite of attention to the indicated causes of his asthma, he was not doing well and

was unable to work most of the time. In January 1940 he was tested with the proteose preparations and gave a good positive reaction to the primary proteose of milk whey and a slight reaction to the secondary proteose. Passive transfer with his serum was likewise positive on a normal test-subject.

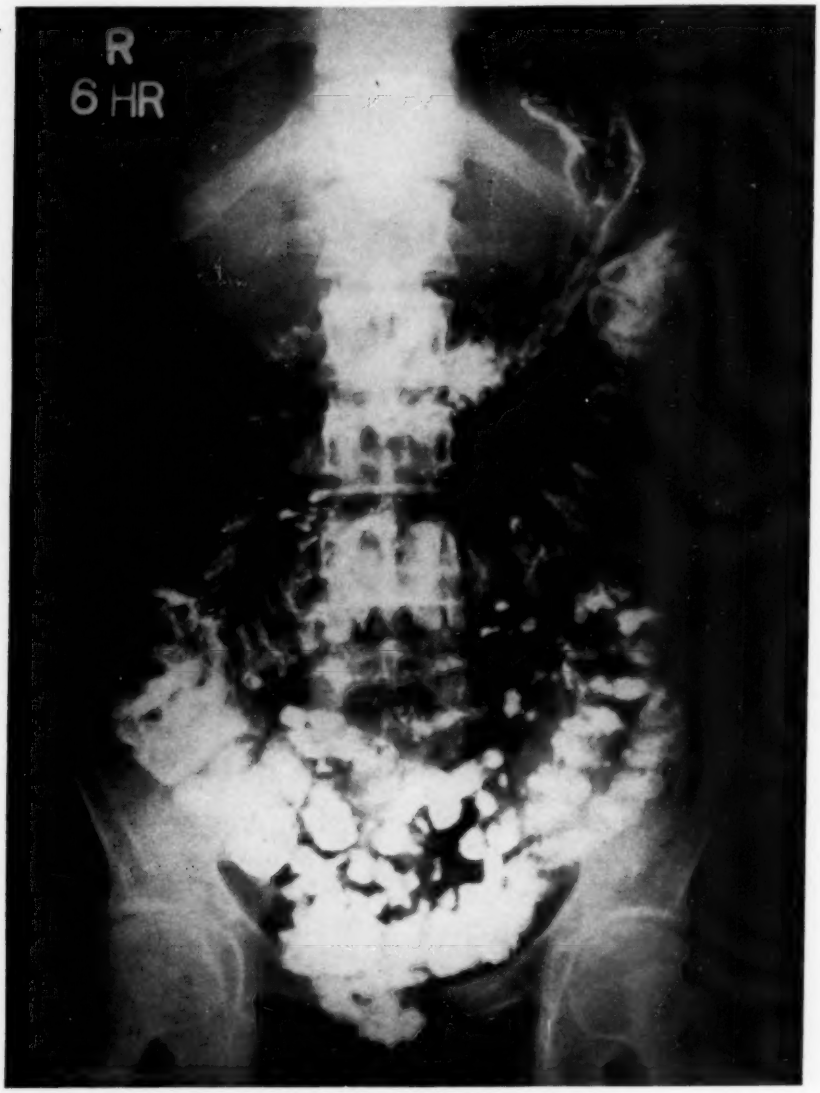


FIG. 3. Six hours after barium and milk.

Later on he was admitted to the hospital for observation. On a certain day when free of asthma he was given a quart of milk to drink—in two hours he developed nausea, then mild asthma, later he had abdominal pain and several loose stools. His asthma increased and lasted 12 hours. This clinical trial

was made on two other occasions with the same results. As evidence of asthma, in addition to physical signs, is the fact that on one day before having milk the vital capacity was 2580 c.c., whereas 5½ hours after having milk it was only 1220 c.c. Gastrointestinal roentgen-rays were made without and with milk in the barium meal. The contrast was definite. Dr. Boone's report says that "Without milk the six hour film (figure 2) shows the stomach empty, with the head of the barium meal in the transverse colon." The six hour film after milk-barium (figure 3) shows "increased motility of the meal in the small bowel. There is considerable residue in the stomach. The entire colon was outlined as early as four hours." Abnormal segmentation of the small intestine was a definite feature.

Thus it seems to me it has been shown that clinical sensitization to protein digestion derivatives, at least at the proteose stage, exists. This helps to explain the "delayed" type of food reactions as previously postulated and suggests a method of approach in the diagnosis of a certain limited number of food allergies.

Nucleic Acid

Another protein derivative that may be briefly mentioned is nucleic acid, which is commanding the attention of immunologists on account of its bearing on serological reactivity. This would not call for special mention here were it not for the recent findings of Winkenwerder, Buell and Howard [30] that 50 ragweed pollen sensitive patients gave typical immediate wheal-erythema reactions when tested with dilute solutions of nucleic acids and many of their derivatives. The skin sensitizing antibody was found in the serum of 10 of their patients by the method of passive transfer, and two patients had typical severe constitutional reactions from the skin test. Sherman, in my clinic, has tried out this test and observed reactions in certain ragweed sensitive patients. The significance of this sensitivity is not at all clear as yet. It is tempting but unwise to stress the importance of such findings or theorize on their possible clinical application.

In closing let me say that I have tried to present some picture of present day trends in the study of allergy. Protein derivatives which a few years ago were considered devoid of antigenic or hapten significance are now found to be of some importance. Studies are proceeding in an attempt to determine the chemical basis of allergic reactions as well as the serological evidence for and the chemistry of the induced immunity.

REFERENCES

1. Dale, Sir Henry H.: Capillary poisons and shock; anaphylaxis; chemical structure and physiological action, Bull. Johns Hopkins Hosp., 1920, xxxi, 257, 310, and 373.
2. Barsoum, G. S., and Gaddum, J. H.: The pharmacological estimation of adenosine and histamine in the blood, Jr. Physiol., 1935, lxxxv, 1.
3. Code, C. F.: The quantitative estimation of histamine in the blood, Jr. Physiol., 1937, lxxxix, 257.

4. Dragstedt, Carl A.: Anaphylaxis and allergy, Ann. Int. Med., 1939, xiii, 248.
5. Campbell, Dan H., and Nicoll, Paul A.: Studies on in vitro anaphylaxis and release of an active non-histamine material from sensitized guinea-pig lung, Jr. Immunol., 1940, xxxix, 103.
6. Schild, H.: The reaction of the guinea pig uterus to histamine and anaphylaxis, Jr. Physiol., 1936, lxxxvi, 51.
7. Menkin, Valy: Studies on inflammation. XII. Mechanism of increased capillary permeability. A critique of the histamine hypothesis, Jr. Exper. Med., 1936, lxiv, 485.
8. Lewis, Sir T.: The blood vessels of the human skin and their responses, 1927, Shaw and Sons Ltd., London.
9. Menkin, Valy: Studies on inflammation. XIV. Isolation of the factor concerned with increased capillary permeability in injury, Jr. Exper. Med., 1938, lxvii, 129.
10. Alexander, H. L.: Treatment of allergic disorders with histamine and histaminase, Jr. Lab. and Clin. Med., 1940, xxvi, 110.
11. Alexander, H. L.: Allergic syndromes in the absence of allergens, Jr. Allergy, 1940, xi, 163.
12. Farmer, Lawrence: Histamine in anaphylaxis and allergy, Bull. New York Acad. Med., 1940, xvi, 618.
13. Gotsch, K.: Hyperergische Phaenomene und Histamine, Ztschr. f. klin. Med., 1936, cxxix, 593.
14. Lass, E.: Jod- und Histaminempfindlichkeit der Haut bei Tuberkuloesen, Ztschr. f. Tuberk., 1933, lxvii, 350.
15. Landsteiner, Karl: The specificity of serological reactions, 1936, Charles C. Thomas, Baltimore.
16. Fink, E. B.: The antigenic properties of proteoses, Jr. Infect. Dis., 1919, xxv, 97.
17. Zunz, M.: Nouvelles récherches sur l'anaphylaxie par les protéoses et les autres produits de désintégration de protéines, Bull. Acad. roy. de méd. de Belgique, 1923, iii, 426.
18. Gay, F. P., and others: Agents of disease and host resistance, 1935, Charles C. Thomas, Baltimore, p. 335.
19. Zinsser, Hans, Enders, J. F., and Fothergill, L. D.: Immunity principles and application in medicine and public health, 1939, The Macmillan Co., New York, p. 33.
20. Jones, F. G., and Moss, J. M.: Studies on tetanus toxoid: 1. Antitoxic titer of human subjects following immunization with tetanus toxoid and tetanus alum precipitated toxoid, Jr. Immunol., 1936, xxx, 115.
21. Hall, W. W.: Active immunization against tetanus with tetanus toxoid, Mil. Surg., 1937, lxxx, 105.
22. Gold, H.: Active immunization of allergic individuals against tetanus by means of tetanus toxoid, alum precipitated refined, Jr. Allergy, 1938, ix, 545.
23. Parish, H. J., and Oakley, C. L.: Anaphylaxis after injection of tetanus toxoid, report of a case, Brit. Med. Jr., 1940, i, 294.
24. Whittingham, H. E.: Anaphylaxis following administration of tetanus toxoid, Brit. Med. Jr., 1940, i, 292.
25. Cunningham, A. A.: Anaphylaxis after an injection of tetanus toxoid, Brit. Med. Jr., 1940, ii, 522.
26. Cooke, R. A., Hampton, S. F., Sherman, W. B., and Stull, A.: Allergy induced by immunization with tetanus toxoid, Jr. Am. Med. Assoc., 1940, cxiv, 1854.
27. Stull, A., and Hampton, S. F.: Antigenic studies of proteoses, Jr. Immunol., 1941, xli, 143.
28. Cooke, R. A.: The delayed type of allergic reaction, Ann. Int. Med., 1930, iii, 658.
29. Cooke, R. A.: Gastrointestinal manifestations of allergy, Bull. New York Acad. Med., 1933, ix, 15.
30. Winkenwerder, W. L., Buell, M. V., and Howard, J. E.: The sensitizing properties of the nucleic acids and their derivatives, Science, 1939, xc, 2337.

THE TREATMENT OF ACUTE CARBON TETRACHLORIDE POISONING WITH A REPORT OF TWO CASES *

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The purpose of this paper is four-fold: (1) to present two cases of acute carbon tetrachloride poisoning (one fatal, with autopsy); (2) to discuss the treatment of this condition; (3) to call attention to the health hazard involved in its widespread use; and (4) to suggest that it be included in textbooks as a disease entity.

Case Reports

Case 1. A nine-year-old boy, who had smeared red chalk on the covers of his bed, took a tin of cleaning fluid from the cupboard and in the process of cleaning found that he liked the odor of the fluid and the way it made him feel. He poured a considerable amount on the blanket, replaced the tin and crawled into bed. He said that he saw stars and then couldn't remember anything. When his father entered the room a few minutes later he found the boy under the covers, completely unconscious and breathing noisily. The physician, on arrival, found the child unconscious, his face flushed, perspiring moderately, pupils dilated, pulse rapid and thready, and all deep and superficial reflexes absent. No clue could be found as to what had happened to him. No medicine bottles were found in the room, and there was no evidence that the medicine chest had been disturbed. His stomach was washed out; three grains of caffein sodium benzoate were given hypodermically; and he was kept warm. In about one hour he became restless. He was catheterized, and the urine showed two plus sugar. Fifteen units of insulin were given. In another hour he had begun to regain consciousness, but as the diagnosis was not clear he was moved to the Nassau Hospital where 15 more units of insulin were given. Soon after, he was able to tell the story of what had happened, and it was evident that he had been anesthetized by carbon tetrachloride as was proved later by inspection of the container. Physical examination at this time revealed nothing further except an area of hyperemia on the outer mid-thigh to mid-calf region of one leg.

Course of Disease

He was in the hospital six days. Immediately on admission blood examination showed a CO_2 content of 48 volumes per cent and 213 mg. per cent of sugar. The urine showed 1.4 per cent sugar and a trace of acetone. He was given 1000 c.c. of normal saline intravenously. He vomited persistently and after a few hours was given a colonic irrigation and 750 c.c. of 5 per cent glucose in saline intravenously. In 12 hours the vomiting stopped and he vomited only twice subsequently. During the first day he was drowsy much of the time and was irritable when awake. That evening his temperature rose to 104.5° F., pulse 120, respirations 28. The temperature stayed around 104° for 16 hours, then fell to 100.5°. The subsequent evening temperatures were 100° F. The blood calcium determination, 16 hours after the onset, was 12.9 mg., so calcium was not given intravenously, but 60 grains a day were given by mouth. As he took fluids well after the first day, no more were given intra-

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From the medical service of the Nassau Hospital, Mineola, Long Island.

venously. Thirty grains of sodium chloride were given four times a day for two days.

On the first day there was tenderness and some rigidity over the upper abdomen and considerable distention. On the second day the liver edge could be felt about 4 cm. below the costal margin, the sclerae were slightly yellow, and a trace of bile appeared in the urine. The tenderness and rigidity in this area persisted, gradually improving until, on discharge, enlargement and tenderness of the liver were the only positive physical signs. Pain and distress in the upper abdomen which were marked during the first two or three days slowly improved. The superficial burn on the leg and thigh was dressed. On the second day the diet consisted of fluids; water, fruit juices to which lactose was added, and gingerale. On the third day he was started on a diet of carbohydrate 350 gm., protein 75 gm., and fat 50 gm., which was continued.

On returning home, the child was kept in bed for three weeks because of the persistence of liver enlargement and a slight evening elevation of temperature. A high carbohydrate diet was continued and he received no other treatment. The liver could not be palpated after one month, so, in spite of the fever, the child was allowed up. It was found that after slight exercise the temperature rose to 100° F., 100.5° F., and, on one or two occasions, a little higher, so his exercise was increased very gradually. No cause, other than exertion, could be found to account for the fever. His activity was slowly increased until, after three months, he was leading a normal life.

Laboratory Findings

Urine. While in the hospital nine specimens were examined. Only the first showed sugar. On five occasions one plus albumin was present and on three occasions a few casts were found. Red blood cells were found only once. Bile was present from the second day to the sixth day. After returning home six specimens were examined, the last on September 15, and always found to be normal.

	Hemoglobin	Red blood cells	White blood cells	Polymorphonuclear leukocytes	Eosinophiles
First day	95%	5.8	22,400	93%	
Third day	100%	5.3	12,100	52%	4
Twelfth day	80%	4.6	6,400	78%	
Twenty-first day	76%	4.8	6,200	68%	

Blood Sugar. On admission the blood sugar was 213 mg.; eight hours later 90.9 mg.; second day 119 mg.; fourth day 111 mg.; twelfth day 80 mg. Blood CO_2 determinations were 48, 46, 38, 48 respectively. Icteric index was 8 and 7.2. Blood calcium was 12.9 mg. on the first day. Blood sedimentation rate on the twelfth day was 18 mm. per hour, and on the twenty-first day, 14 mm. per hour. A roentgen-ray of the lungs was normal on the seventeenth day.

Discussion

This boy received a large dose of carbon tetrachloride by inhalation. He was completely anesthetized for over two hours. It is possible that there was also absorption through the skin, as there later appeared a large area of hyperemia and burn on the thigh and leg which had been in contact with the wet bed covers. In the absence of history, when sugar was found in the urine, diabetic coma was considered a possibility. It was not until the

second day that definite evidence of liver damage occurred, i.e., an enlarged, tender, painful liver, a trace of bile in the urine, high fever and leukocytosis. The importance of early intravenous administration of calcium and glucose was not appreciated, and since the blood calcium was high calcium was given only by mouth. Fluids and medication given by mouth were nearly all retained after the first day. There was very little evidence of kidney damage. No central nervous symptoms occurred. The management of the case after the acute phase was determined by the results of tests which showed the degree of liver repair. Liver tenderness persisted for two weeks and enlargement for a month. These physical signs, plus evening fever, increase in polymorphonuclear leukocytes in the blood, and a slightly elevated blood sedimentation rate indicated that repair was not complete in three weeks. During the next six weeks an elevation of temperature to between 100° F. and 101° F. on slight exercise indicated continued disturbance, as no other cause could be found for this fever.

Case 2. A 48-year-old carpenter was admitted to the hospital after having drunk a cleaning fluid containing carbon tetrachloride. His past history was negative except that he was a steady consumer of alcohol. In fact, when the accident occurred he had been drinking and in the dark poured another drink from the wrong bottle. Almost at once he began to vomit persistently, followed by diarrhea which later produced "very dark colored" stools. He felt as though he had a fever and was very drowsy. At times he was delirious. The day before admission he noticed that his abdomen was markedly enlarged. He had not urinated for three days. He had been treated at home symptomatically, and had been given glucose twice intravenously after he became anuric.

He was admitted to the hospital on the eighth day of his illness. Physical examination showed an obese, intensely jaundiced, critically ill man. He was quite stuporous and responded to questioning with difficulty. His legs and ankles showed a two plus edema. His pharynx was injected and slightly edematous. There was a systolic murmur localized at the apex. Blood pressure was 160 mm. Hg systolic and 80 mm. diastolic. His abdomen was greatly distended, with signs of fluid, and there was tenderness over the liver region.

He was in the hospital 44 hours, dying on the tenth day of his illness. He grew steadily worse, becoming cyanotic and comatose on the second day. His temperature was never over 100° F. The pulse varied between 72 and 118. His respirations were labored and the rate around 30 per minute. He had no twitching or convulsions. He vomited once, a large amount of coffee-ground material. He was catheterized at once on admission, and 30 c.c. of dark colored urine were obtained which showed three plus albumin, sugar 0.4 per cent, bile three plus, and microscopically many fine and coarsely granular and hyaline casts, 10 to 15 red blood cells and eight to 10 white blood cells, per high power field. Blood non-protein nitrogen was 160 mg., sugar 222 mg., creatinine 6 mg., icteric index 100, CO_2 35 vol. per cent. Blood count: hemoglobin 85 per cent, red blood cells 3.3 million, white blood cells 10,300 with 81 per cent polymorphonuclear leukocytes.

Treatment

Soon after admission he was given a colonic irrigation which returned a "dark black liquid." He received five intravenous injections of 50 c.c. of 50 per cent glucose, each of which was followed by 25 units of regular insulin. He was given

daily 1200 c.c. of fluids by mouth including water, fruit juices and milk. He vomited only once so most of this was retained. He was catheterized on the second day, and only 3 c.c. were obtained. An abdominal paracentesis was attempted on the second day, but, for some reason, no fluid was obtained. He did not void any urine while in the hospital. Oxygen was administered on the second day.

An autopsy was performed with the following positive findings. The skin and sclerae were deeply jaundiced. There was a large amount of bile-stained fluid in

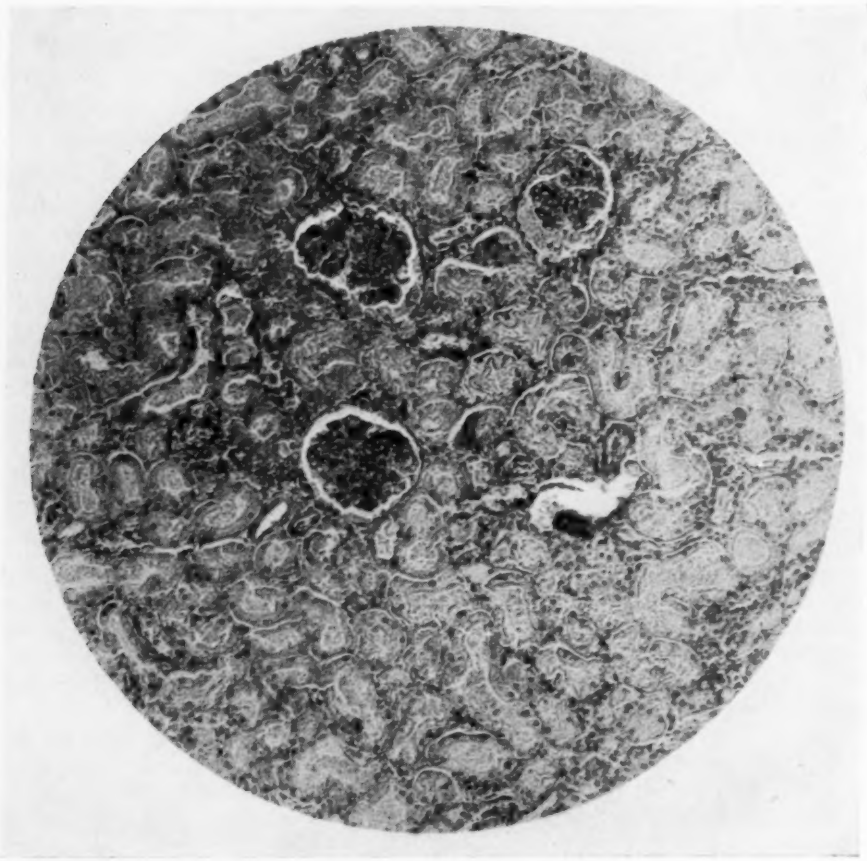

FIG. 1. Kidney (× 50)—showing cloudy swelling and necrosis of the tubular epithelium. The glomerulus in the upper right segment shows albuminous exudate in the intracapsular space.

the abdominal cavity. The epicardium was somewhat congested and showed scattered petechial hemorrhages. The liver weighed 2350 gm., and was pale brown in color. On section the cut surfaces presented numerous hemorrhagic areas in which the normal pattern was indistinct. The spleen weighed 390 gm., and the pulp was mushy. The adrenals appeared normal. The kidneys weighed 300 and 290 gm.; the capsules stripped with difficulty; the cut surfaces were grossly congested and contained numerous hemorrhagic areas as did both pelves. There were extensive petechial hemorrhages in the bladder mucosa. The pancreas also showed a few scattered

hemorrhages. The stomach, the small and large intestines showed numerous scattered hemorrhagic areas. A trace of carbon tetrachloride was found in the brain but not in the liver or kidneys.

Microscopic Examination

Liver. "Sections show extensive pathological change. There are large areas of necrosis with associated hemorrhage; these are located for the most part away

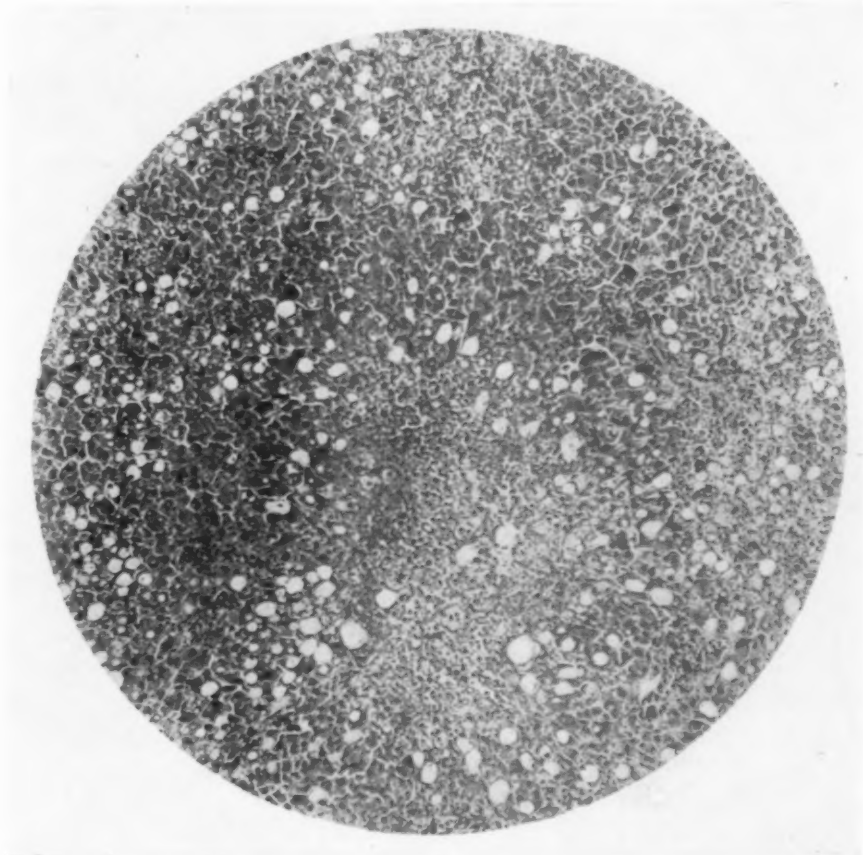

Fig. 2. Liver (× 50)—showing focal necrosis and extensive fatty metamorphosis of the liver cells.

from the portal systems and more toward the center of the lobules. In addition, there is widespread fatty vacuolization of the liver cells. There is a moderate increase of the round cells in the periportal spaces."

Kidney. "Sections show marked degenerative changes in the tubules varying from cloudy swelling to actual necrosis. The glomerular tufts are engorged. The capsular spaces contain albuminous exudate. Some of the glomerular tufts are adherent to the capsule. In an occasional glomerulus, free red cells are seen in the capsular spaces. The blood vessels are normal."

Spleen. "Sections show moderate to marked engorgement of the pulp with red cells. Many irregular particles of extracellular brown pigment are present. The follicles are normal."

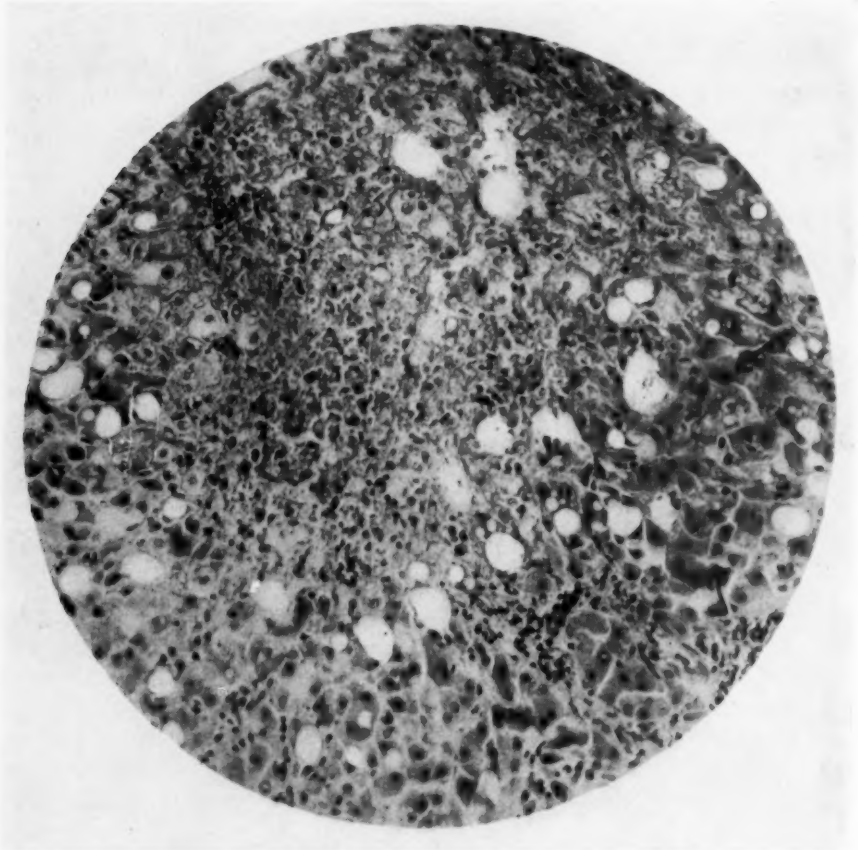

FIG. 3. Liver (× 250)—showing higher magnification of necrotic zones. The large hyperchromatic nuclei (arrow) suggest regenerative changes.*

DISCUSSION

This man was reported to have drunk a "furniture polish" used for cleaning purposes. Due to unusual circumstances surrounding the case the exact nature of this fluid was not known and it was labeled with an unfamiliar trade name. The medical examiner recovered the original container and found it to have a high carbon tetrachloride content. The man was an alcoholic and had been imbibing before he drank the fatal portion thinking it to be whiskey. Its toxicity was undoubtedly increased by alcohol. It was also taken after he had eaten, which again made it more toxic. When

*I am indebted to Dr. Theodore J. Curphey, Medical Examiner of Nassau County, for his interpretation of the pathological findings; and to Mr. David Skelton, staff photographer, for the photomicrographs.

he reached the hospital on the eighth day, he presented an extreme picture of acute gastroenteritis, hepatitis and nephritis. The autopsy confirmed the clinical findings showing degenerative changes in the liver with a marked central necrosis, involvement of both the glomeruli and tubules of the kidneys, and extensive hemorrhage into the mucosa of the gastrointestinal tract and in other organs. These are the typical end result of this type of poisoning.

Treatment of Acute Carbon Tetrachloride Poisoning

Two drugs, calcium and glucose, are definitely indicated in the treatment of carbon tetrachloride poisoning. The importance of this treatment does not seem to be generally recognized as was shown in the management of the two cases herein reported.

What is the rôle of calcium in the treatment of this condition? The following investigators have contributed to our knowledge of this subject. Lamson, Minot and Robbins [1] from experiments on dogs found that carbon tetrachloride was much more toxic and caused greater liver damage in animals fed on a low calcium diet than in those fed on a normal or high calcium diet. They also showed that symptoms of intoxication were promptly relieved by the intravenous administration of calcium. They thought that the central necrosis of liver cells increased the bilirubin in the blood and that bilirubin entered into a complex combination with calcium. Thus, though the total blood calcium be normal or high, the active or ionized calcium may be low. Symptoms of lack of available calcium sometimes ensued, such as tremors, convulsions, tetany and tendency to hemorrhage.

Wokes [2] fed mice on low and high calcium diets plus cod liver oil and found little difference in the response of the two series after giving a toxic dose of carbon tetrachloride. He did find, however, that calcium given one hour before administration reduced the mortality but did not completely protect the liver.

Cutler,[3] in studies on large series of dogs, found that in 131 animals fed on a diet of lean meat without bones, 98 died after a toxic dose of carbon tetrachloride; whereas, in 98 dogs fed on lean meat and calcium salts, only 18 died. All showed in a few hours an increase in guanidine in the blood and subsequent hypoglycemia. To protect against intoxication they suggest that a diet should not tend to increase guanidine as does meat, should be rich in calcium to combat hyperguanidinemia, and high in carbohydrate to relieve hypoglycemia. Minot [4] demonstrated a similar increase in guanidine in the blood followed by hypoglycemia after liver injury, and showed that symptoms of guanidine intoxication are similar to those of carbon tetrachloride poisoning. He discussed the effect of this guanidine accumulation on the carbohydrate metabolism and found that the administration of calcium salts hastened recovery. The giving of glucose alone did not prevent death in experimental animals, but calcium did. He concluded that the exact mechanism of this beneficial action of calcium is not known.

It seems, therefore, that calcium plays an important rôle in protecting against liver damage and curing symptoms of intoxication from carbon tetrachloride. It would appear rational to administer calcium and glucose as soon as the diagnosis is made and continue it until all evidences of liver damage have disappeared. Even in the absence of signs of liver damage calcium should be given for four or five days. A normal blood calcium does not mean that calcium is not needed, for in this condition part of the diffusible or usable calcium may combine in some non-usable form and still be present in the blood. Calcium therapy has been successfully applied in several cases reported in the literature.

How should calcium be administered? In dealing with a normal digestive apparatus it would seem that giving calcium by mouth every four to six hours would maintain an adequate blood level. In acute carbon tetrachloride poisoning with involvement of the gastrointestinal tract and liver the absorption is not normal, and even though food is retained we do not know how it is utilized. Therefore, essential fluids, hypertonic glucose and calcium should be given intravenously, at least until we know that they can be absorbed from the intestinal tract. In severe cases this should be done every five or six hours, the interval lengthened as the patient is able to take and assimilate fluids and food. If nephritis is present and edema appears, making it necessary to limit fluids, a small amount of a higher concentration of glucose (50 c.c. of a 50 per cent solution) should be given. If jaundice and signs of liver involvement occur, the intravenous route should be used if necessary for from one to two weeks. Blood chemical studies will materially help in ascertaining the degree of liver and kidney damage and so determine when treatment can be safely terminated.

It is also important to know how soon liver damage occurs and when liver cell repair is complete. The liver has great regenerative ability and functions efficiently if a small part of it remains normal, as was shown by Bollman and Mann.[5] Lacquet,[6] and Cameron and Karunaratne[7] have studied the rate of liver destruction and repair in rats. After administering a toxic dose of carbon tetrachloride, destructive changes begin in a few hours, becoming extensive in 24 hours and continuing so for three or four days. In three to five days signs of regeneration can be seen and after two weeks repair is complete.

Peery[8] had occasion to observe autopsies of three patients who simultaneously drank carbon tetrachloride. One died in six hours and showed no change in the liver; the second died in 68 hours and showed extensive necrosis and hemorrhage; and the third died after 150 hours showing extensive damage but evidences of regeneration taking place. In our inhalation case the liver was swollen and tender on the second day when a trace of bile appeared in the urine. Two or three days may elapse before liver damage manifests itself so it is better to assume that liver damage exists and treat it at once.

Earlier writers made little mention of kidney damage, although it oc-

curred in some of the cases reported. Franco,[9] in 1936, called attention to the frequency of kidney involvement and reviewed the literature with respect to this point. Other cases have since been reported and Semetra[10] in 1939, from a collected series of 141 cases found that 33 gave clinical evidence of renal involvement, and 17 of the 25 autopsies showed anatomical evidences of renal disease. Both of our cases showed signs of kidney involvement. Case 2 showed extensive damage at autopsy. As far as treatment of the kidney is concerned, no conflict in the choice of therapy arises because of the involvement of both liver and kidney. Stomach lavage, colonic irrigation, forcing of fluids and glucose and calcium intravenously all tend to protect the kidney and constitute sound treatment should serious kidney damage be present.

If hemorrhage into the gastrointestinal tract occurs, especially if associated with liver damage and lowered fibrinogen, calcium is useful. If there is considerable blood lost, transfusion with blood or blood plasma is indicated.

Eye symptoms, such as blurred vision and toxic amblyopia, have been described from carbon tetrachloride intoxication but disappear as the intoxication is combated.

Forbes and Neale[11] demonstrated a substance isolated from liver extract which protected rat livers against necrosis following carbon tetrachloride inhalation. With their associates[12, 13, 14] they later showed this substance to be sodium xanthine and found that other purines gave like protection. This action of xanthine was confirmed by Barrett, MacLean and McHenry,[15] and Fitzhugh.[16] Whether this principle is applicable to human liver disease remains to be demonstrated, but it would seem to be of potential value. Dr. Forbes in a personal communication states that he has used xanthine in one case of phosphorus poisoning and felt that it played a great part in the patient's recovery. Since it takes from 24 to 48 hours for xanthine to exert its maximum protective action, its action, if given after exposure, would be merely to help accelerate repair.

Outline of Treatment

1. Remove unabsorbed carbon tetrachloride from the gastrointestinal tract by stomach lavage, and colonic irrigation.

2. Force fluids by mouth and intravenously to dilute and wash out carbon tetrachloride and toxic products.

3. Prevent or treat signs of intoxication and organic damage by:

a. 10 to 15 c.c. of 10 per cent calcium gluconate intravenously every five or six hours the first two days, then two to four times a day depending on severity.

b. Hypertonic glucose intravenously two to four times daily.

c. High carbohydrate, low fat and low protein diet.

d. 20 grains of calcium gluconate by mouth every four hours.

4. Transfuse with blood or blood plasma if there has been much loss of blood.

5. Repeat blood chemical determinations until blood returns to normal.

6. Rest in bed until evidences of liver and kidney damage have disappeared.

Carbon Tetrachloride as a Health Hazard

In 1933, 30,343,693 pounds of carbon tetrachloride were used in this country and in 1938, 77,975,057 pounds were used. This widespread use of carbon tetrachloride presents a definite health hazard. In industry this hazard has been recognized and largely controlled. Great industries (chemical and drug, rubber, paint, fire extinguisher, and dry cleaning), in which this substance is used extensively, have studied the problem and have taken steps to protect workers from acute and chronic poisoning. Investigations by Smyth and Smyth,[17] Davis,[18] and others interested in industrial medicine illustrate the type of research responsible for these improved conditions. Smyth[19] pointed out that considering the enormous quantity of carbon tetrachloride used in industry there have been suprisingly few casualties. He bases his opinion partly on the small number of cases reported in the literature and partly on reports from insurance companies, health departments and departments of labor and industry. He could find only 122 acute and subacute cases reported, 27 of these being fatal. Of the 27 fatal cases, 14 were due to the use of carbon tetrachloride as an anthelmintic. Semetra,[10] in 1939, collected a series of 141 cases, 39 of them fatal. Cases reported in the literature probably represent only a small percentage of the total cases occurring. Carbon tetrachloride poisoning is not a disease reportable to health departments, and cases dying a few days after poisoning may have been recorded as acute hepatitis or acute nephritis, without mention of carbon tetrachloride. In fact, in some instances it may not have been known that carbon tetrachloride was the offending agent because the label on the container made no mention of the contents. In reviewing the case reports, but few acute cases occurred in industrial plants, which proves that care and education of workers have reduced the risk where its use is supervised.

In medicine carbon tetrachloride is used internally only as an anthelmintic, principally in the treatment of hookworm, and externally to cleanse the skin. If the patient is properly prepared before the drug is administered and it is given on an empty stomach there is little risk in using it.

In nearly every home can be found a can or bottle containing one of the many brands of cleaning fluid containing carbon tetrachloride. Thousands of small clothes cleaning, and hat and shoe cleaning establishments use carbon tetrachloride daily; many of the users do not know what they are using and use it carelessly. One large New York department store sells 11 different brands of cleaning fluid containing carbon tetrachloride. Our neighborhood drugstore sells five.

The Federal Security Agency, Food and Drug Administration, states that there is no federal law which specifically requires warnings to appear on the labeling of products of this type. The Federal Food, Drug and Cosmetic Act does not regulate cleaning fluids other than those considered cosmetics. Section 502 requires the proper labeling of "drugs or devices" but cleaning fluids are apparently not so considered.

It is the custom of many of the manufacturers of these products to include a warning on the label to the effect that it should be used in a well ventilated room or near an open window. The character and presence of a warning seem to be at the discretion of the producer rather than dictated by law.

Is this type of warning sufficient? The warning usually appears in small print inconspicuously placed on the label. In fact, statements as to the safety of the product, because of its non-inflammable nature, are often emphasized giving a sense of false security. One product seen in a small hat cleaning establishment had this notice printed in large type on the front of the container—"Non-Explosive, contains no acid. Safe for fabric. Safe for you. Here at last a real spot remover!" On the side of this container, at the bottom of the instructions as to its various uses, in the same sized small type, appears the following: "Volatile solvent. Use with adequate ventilation. Avoid prolonged breathing of vapor." The proprietor of this shop said he had never seen this warning or known that it contained a poisonous substance and had, on occasions, noticed that he became light-headed and had a headache after using it. Daily exposure of this nature may cause chronic liver damage.

If an adequate, conspicuously placed warning to the effect that the fluid is poisonous if inhaled or drunk were placed on the container it would be used with greater care and kept in a safe place. In the first case here reported, if the parents had appreciated the nature of the cleaning fluid it would not have been left in an accessible place within easy reach of a curious child; and in the second case the fluid would not have been carelessly poured into a whiskey bottle which still bore the whiskey label. Nearly every case reported in the literature could have been prevented if the purchaser had appreciated the fact that the product was poisonous. The following excerpts from case reports illustrate this: School janitor died in four days of liver symptoms after applying floor wax; maid cleaning dress in cleaning fluid found dead beside basin; man cleaning old telephones became sick; man drank fluid by mistake and died; woman overcome washing hair; man overcome spraying room with cleaning fluid; man painting brewery vat with preparation containing carbon tetrachloride; two year old boy swallowed fluid; woman cleaning dress in closed room; man cleaning furniture and draperies; dry cleaner overcome; three negroes drank cleaning fluid from can on garbage dump—all died; five sailors overcome by fumes moving tins in store room; three students ill after cleaning ink pads on printing press.

It would not be necessary to frighten the buyer by requiring a skull and crossbones type of label, but an adequate warning could be prescribed by law which would not interfere with the sale of this useful product, but would be fair to both buyer and seller. The contents of the product should be stated on the label! Public health education by our health departments and those interested in preventing disease is worth consideration. Use of carbon tetrachloride in industry is being made safer through education and protective devices. Proper labeling and education can render the same degree of protection to all users, for it is definitely a preventable disease.

An editorial in the Journal of the American Medical Association [20] entitled "Volatile Poisons in the American Home" stresses the importance of this type of health hazard and warns against the careless use of such substances. The fact that carbon tetrachloride masquerades under a host of trade names without its presence being indicated is responsible for many mishaps.

Carbon Tetrachloride Poisoning: A Disease Entity

In treating unusual diseases with which the physician is not familiar, two procedures are open to him; to turn to books and read up the subject, or to seek help from someone who is familiar with it. Both procedures were resorted to in our first case. In no accessible textbook could any useful information be found. Two consultants were called and considerable difficulty was encountered in finding someone familiar with this condition. It is evident from the case reports in the literature that in many cases the essential procedures of proper treatment were not applied.

In reviewing many of the latest editions of our standard textbooks of medicine, therapeutics and toxicology, not one was found which described carbon tetrachloride poisoning as a disease entity. Carbon monoxide, phosphorus and bichloride of mercury poisoning were so considered but not carbon tetrachloride. The symptomatology, pathology and treatment of this poisoning are definite and its incidence sufficient to warrant its recognition. The writers of textbooks should include carbon tetrachloride poisoning in the table of contents.

Summary

1. Two cases of acute carbon tetrachloride poisoning have been presented. The first, a nine year old boy receiving a large dose by inhalation showed evidence of liver and kidney damage, followed by a slow convalescence. The second, a 48 year old man, an alcoholic, after drinking cleaning fluid died after 10 days' illness during which he presented symptoms and signs of extensive damage to the liver, kidneys and gastrointestinal tract. An autopsy confirmed these findings.

2. The treatment of this condition is discussed, especially the importance

of immediate and continued administration of calcium and glucose until evidences of intoxication and organic damage have disappeared.

3. That carbon tetrachloride poisoning presents a definite health hazard is demonstrated. Laws requiring the proper labeling of products containing carbon tetrachloride are urged, and education of its users is suggested.

4. A plea is made to the writers of textbooks to consider carbon tetrachloride poisoning a disease entity, thus making knowledge of its nature and treatment accessible.

BIBLIOGRAPHY

1. Lamson, P. D., Minot, A. S., and Robbins, B. H.: Prevention and treatment of carbon tetrachloride intoxication, Jr. Am. Med. Assoc., 1928, xc, 345–349.
2. Wokes, F.: Effect of calcium administration on carbon tetrachloride toxicity in mice, Quart. Jr. Pharm. and Pharmacol., 1933, vi, 413–417.
3. Cutler, J. T.: The influence of diet on carbon tetrachloride poisoning in dogs, Jr. Pharmacol. and Exper. Therap., 1932, xlv, 209–226.
4. Minot, A. S.: Mechanism of hypoglycemia produced by guanidine and carbon tetrachloride poisoning, Jr. Pharmacol. and Exper. Therap., 1931, xliii, 295–313.
5. Bollman, J. L., and Mann, F. C.: Experimentally produced lesions of the liver, Ann. Int. Med., 1931, v, 699–712.
6. Lacquet, A. M.: Experimental pathology of the liver: effects of carbon tetrachloride on normal and on restored liver after hepatectomy, Arch. Path., 1932, xiv, 164–176.
7. Cameron, R., and Karunaratne, W. A. E.: Carbon tetrachloride cirrhosis in relation to liver regeneration, Jr. Path. and Bact., 1936, xlii, 1–21.
8. Peery, T. M.: A study of carbon tetrachloride poisoning: stages of hepatic damage and repair in man, Arch. Path., 1938, xxvi, 923–941.
9. Franco, S.: Nephritic syndromes caused by industrial poisoning with carbon tetrachloride, New York State Jr. Med., 1936, xxxvi, 1847–1853.
10. Semetra, H.: Nephrosis due to carbon tetrachloride, Arch. Int. Med., 1939, lxiii, 760–777.
11. Forbes, J. C., and Neale, R. C.: A new preparation protecting against rat liver necrosis, Proc. Soc. Exper. Biol. and Med., 1936, xxxiv, 319–320.
12. Forbes, J. C.: Studies on the prevention of liver cirrhosis by the sub-cutaneous injections of xanthine containing preparations, Jr. Pharmacol. and Exper. Therap., 1939, lxv, 287–293.
13. Neale, R. C., and Winter, H. C.: Identification of active crystalline substance from liver which protects against liver damage due to chloroform or carbon tetrachloride: Study of related compounds, Jr. Pharmacol. and Exper. Therap., 1938, lxii, 127–148.
14. Forbes, J. C., and Outhouse, E. L.: Studies on the mechanism of the protective action of xanthine against carbon tetrachloride poisoning, Jr. Pharmacol. and Exper. Therap., 1940, lxviii, 185–193.
15. Barrett, H. M., MacLean, D. L., and McHenry, E. W.: Experiments with an "anti-narcotic" material prepared from liver, Jr. Pharmacol. and Exper. Therap., 1938, lxiv, 131–137.
16. Fitzhugh, O. G.: Liver regeneration in rats protected with xanthine against carbon tetrachloride poisoning, Proc. Soc. Exper. Biol. and Med., 1939, xl, 11–15.
17. Smyth, H. F., and Smyth, H. F., Jr.: Safe practices in the industrial use of carbon tetrachloride, Jr. Am. Med. Assoc., 1936, cvii, 1683–1687.
18. Davis, P. A.: Carbon tetrachloride as an industrial hazard, Jr. Am. Med. Assoc., 1934, ciii, 962–966.
19. Smyth, H. F.: Carbon tetrachloride in industry, Indust. Med., 1935, iv, 12–15.
20. Volatile poisons in the American home: Editorial, Jr. Am. Med. Assoc., 1933, ci, 1238–1239.

A THEORY CONCERNING THE MANNER IN WHICH THE STOMACH EMPTIES ITSELF*

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The actual mechanics of how the stomach empties have never been explained in a perfectly clear fashion. The descriptions of this important function vary considerably in every textbook on physiology, and appear to be vague and incomplete. Cannon believes that the acidity of the chyme controls the pyloric sphincter, that a certain degree of acidity in the stomach causes it to open, and that increased acidity in the duodenum causes it to empty. There is also another factor which comes into play, namely, that mechanical stimulation on the stomach side causes the pylorus to open and that mechanical stimulation on the duodenal side causes it to close, and that as long as material stays in the cap the pylorus remains closed. The peristaltic waves tend to vary in intensity, and when a strong wave passes over the antrum it tends to open the cap and to raise the pressure in the antrum so that some of the contents of the stomach will pass through the pylorus into the antrum. Before the wave reaches the pylorus it closes. Towards the end of digestion the tone of the sphincter tends to diminish, and the pylorus relaxes so that regurgitation of food from the duodenum to the stomach occurs.

Cole, basing his conclusions upon serial radiography, states that the activity of the sphincter is directly proportional to the magnitude of the antral contractions, and that chyme passes into the duodenum during each of these contractions but not during the intervals.

Wheelon and Thomas claim that, when a peristaltic wave beginning in the body of the stomach reaches the antrum, the sphincter becomes relaxed, and that material swept forward by the constricting wave is free to pass through the opening of the pylorus. The pylorus closes before the wave reaches it and then there is a period in which the antrum and the pylorus are in a contracted state. After this the antrum goes into a negative phase and the pylorus remains in a contracted state.

William Beaumont and later Hofmeister and Schurtz were of the opinion that after a peristaltic wave had passed down the body of the stomach and reached the antrum it became systolic in character, almost dividing the stomach into two halves, the lower part of the wave passing onward to the pylorus.

Starling stated that there is a strong transverse band demarcating the body of the stomach from the antrum. Strong contraction waves in the

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antrum force food toward the pylorus which remains closed, therefore the food can not escape and is forced backward forming an axial reflux stream toward the cardia, which condition permits of thorough mixing. Transitory opening of the pylorus allows a few cubic centimeters of material to be squeezed into the duodenum. Tonic contractions in the fundus produce a steady pressure. The pylorus opens more and more frequently as digestion progresses and the stomach becomes empty.

Howell says that the pylorus relaxes occasionally to allow a contraction wave to eject food into the antrum. This does not occur with each wave.

Wright adds that when empty the walls of the stomach are in rather firm apposition, but when food enters through the cardia the muscle fibers elongate sufficiently to make the cavity conform to the size of its contents. This does not change the internal pressure on the contents to any great extent. A peristaltic wave occurs about every twenty seconds. When the stomach is first filled the pylorus is tonically contracted. In three to twelve minutes the pylorus opens to permit a small quantity of chyme to escape. The pylorus relaxes and opens when a wave reaches the antrum.

Very little is said in the literature concerning the effect of gravity upon the emptying of the stomach, and this force we feel has little, if any, effect. If we take other organs of the body for analogy we find that there is not one that depends upon this force for its proper function. Certainly other parts of the digestive tract seem to operate in any position. The position of the body does not seem to have any effect upon the manner in which the stomach empties itself, for the function goes on just as well in an erect as in a horizontal position, and if horizontal, it makes no difference whether the individual be upon his side, his back or his face. This is true in spite of the fact that the filled stomach changes position to a great extent depending upon what position the body happens to be in and what media fill its lumen. The cardia is fixed, but the pyloric end is fairly movable. When lying upon the left side the pylorus may be to the left of the midline, and when on the right side may be well over on the right side of the abdominal cavity. Even when a person has the foot of his bed elevated on shock blocks, his stomach seems to empty in a satisfactory fashion. Of course one cannot say dogmatically that gravity plays no part whatsoever; certain positions may make emptying a little easier, but the evidence to back up this supposition is very sparse.

Anyone who has watched a stomach filled with a liquid barium medium under a fluoroscope could not have failed to notice that even though there was good, active peristalsis in the antrum, the cap filled only on occasion, and that it was practically impossible to fill the cap by manual manipulation until the stomach was "good and ready." If the stomach is observed patiently over a considerable period at one examination it will be noticed that the peristaltic waves start in the upper portion of the body, are shallow, sluggish and without much force. These waves travel in a caudad direction at the rate of

about one every twenty seconds. When they reach the *incisura angularis*, that is, the beginning of the antrum, they suddenly become deep and forceful and continue toward the pylorus with great regularity, taking about ten seconds to traverse this distance. As the observer watches these waves he will note that suddenly, for no appreciable reason, the antrum takes on a firm, ball-like appearance, and that it is completely divided from the fundus except for perhaps a trickle of barium. This ball seems to contract to a slight degree and as it does so the cap fills and barium is seen to literally shoot through the entire duodenum to the first part of the jejunum. This is best observed at the beginning of the examination, the first time it happens, when the duodenum is empty. After that there is barium scattered throughout the duodenum and this phenomenon is not so apparent. As this occurs the usual peristaltic wave begins just distal to the *incisura angularis* and travels toward the pylorus in the usual fashion. The wave seems a little deeper than usual but this may be only apparent due to the increased tonicity of the antrum. The initial division at the incisura relaxes when the wave is under way. The cap is distended during this first rush of contents into the duodenum and remains so for a comparatively short while. It then takes on a smaller diameter. Peristalsis in the duodenum seems to start just distal to the cap.

This course of events gives one the impression that the material from the stomach is being ejected in a forceful fashion, much more strongly than would be expected from a peristaltic wave travelling at the rate of one centimeter a second. I do not think that a peristaltic wave travelling at this rate of speed, unless it actually occludes the lumen of the hollow structure over which it is travelling, can apply much pressure to the watery contents ahead of it. The old analogy of the sausage skin filled with sausage meat does not apply in this case. In this demonstration the fingers are so placed around the tube as to simulate a constriction band, and then as they are moved along slowly the contents of the tube are forced out ahead of it. This analogy might be true if the contents of the antrum were a semi-solid, as is the sausage meat, but they are not, they are to all intents a liquid. If you repeated this experiment filling the tube with water, very little increase in pressure would be obtained so long as the rate of travel of the constriction band remained slow (one cm. a second), and the lumen of the tube was not entirely constricted. If, however, simulating a rush wave in the intestinal tract, you moved your constricting band forward at a rapid rate, you would push the water ahead of the band in an excellent fashion. Also if you entirely occluded the lumen of the tube with your constricting band, water would be forced out ahead of the band. This is one small piece of evidence that makes us feel that there is more to emptying the stomach than a mere peristaltic wave. What evidence there is points to the fact that the peristaltic waves in the antrum do not entirely occlude the lumen. It might be argued that these waves set up currents in the liquid and that these cur-

rents all tend to go toward the pylorus. However, these currents, of necessity, must be weak and could not produce the rapid ejection of fluid into the duodenum that we have noted.

By means of the gastroscope* a new structure in the stomach has been described by many observers, namely the *musculus sphincter antri.* This structure is a rope-like ridge located upon the greater curvature at right angles to the long axis of the stomach, just opposite to the *incisura angularis,* and it extends about half way upward on the anterior and posterior walls. Although it is seen without exception in every stomach and constitutes part of the first landmark that is used for purposes of orientation, it varies somewhat in each individual, being more pronounced in some and less so in others. It seems to consist of a ridge of muscle covered with normal mucous membrane and derives its rope-like quality from the fact its axis is not quite at right angles to the usual mucosal folds. These folds, which run longitudinally to the long axis of the stomach, traverse the *musculus* at a slightly oblique angle. The *musculus* is not found at post mortem, in the dissecting room or at the time that the stomach is open in the operating room. It does not seem to be differentiated from the rest of the stomach wall histologically. Therefore it would seem that it is physiological or functional in character; that it is a functional structure and has some definite use in the mechanics of the stomach. It is there for a purpose, for if it were vestigial it would probably have long since disappeared. Only once has it been described except in connection with gastroscopic observations, and that was in Germany when two men, who had been electrocuted, were examined at necropsy a few moments after death. Many times during our gastroscopic examinations a spasm has been noted which for the time being impeded the examination of the antral portion of the stomach. These spasms have always caused complete contracture of the lumen of the stomach and have involved this structure, namely the *musculus sphincter antri.* The contracted lumen of the stomach at this point usually has a slit-like appearance rather than a stellate one. The contracted portion of the walls seems to involve the greater curvature and part of the anterior and posterior walls, and not the lesser curvature. We have noted this stricture or spasm on several occasions when we were examining individuals with thin abdominal walls. In such people, when the scope is in place and the examining room very dark, the outlines of the stomach can be seen through the abdominal wall perfectly. When the spasm was noted by the observer at the eye-piece, it was seen that the transilluminated image of the stomach on the abdominal wall had the lower portion cut off, but when the gastroscopist announced that the spasm was relaxed the remaining portion of the stomach was suddenly illuminated suggesting that the antrum had been dis-

* The personal observations herein mentioned were made at St. Luke's Hospital and Knickerbocker Hospital, New York City, in connection with the use of the Wolf-Schindler Flexible Gastroscope in over 750 examinations of the stomach. This work was done between February 1938 and September 1940.

tended at the time of the spasm and that the spasm merely divided the stomach into two portions. It would seem from these observations that the *musculus sphincter antri* had the function of forcibly dividing the stomach into two portions. I say forcibly because the spasm cannot be relieved by distending the stomach with air under some pressure.

The gastroscope has been extremely useful in establishing another fact. In over 700 observations we have seen the pylorus, either in whole or in part, more than 80 per cent of the time. Not once have we seen a pylorus that was not patent. This structure remains open practically all of the time and closes only for a brief interval when the contraction wave from the antrum reaches and blends with it. This has been consistently true and not one exception has been noted, although several times we have noted a pylorus that did not close at all during the examination. In these cases no contraction waves were seen in the antrum. This observation has been so consistent and so uniform that we have felt that it must represent the usual rhythm of the pylorus. In several instances we have examined stomachs that contained a considerable quantity of food. The deep contraction wave can be seen starting in the first portion of the antrum just distal to the *musculus sphincter antri*. It progresses slowly and evenly, as a ring around the antrum, all portions of it reaching the pylorus at the same time. Just as it reaches this structure and blends with it the pylorus closes. It remains closed for about one second and then opens again. The closure of the pylorus does not as a rule take place in a stellate fashion as has been described and pictured in certain books on gastroscopy, that is, with radial folds of mucosa extending from the closed orifice as is the case with the anus. Rather, the tightly closed pylorus might be said to resemble a full blown rose; that is, there is a reflux of loose mucosal folds back toward the stomach, each fold representing the petal of the rose. This is a rather unusual appearing phenomenon, and one difficult to describe, but we feel that it is the usual course of events and that any deviation from it is abnormal. In certain prepyloric lesions we have noted the stellate type of closure. However, the full significance of variations from what we consider normal has not been arrived at. It is interesting to note here that even though we have examined over 20 stomachs in which there were varying degrees of food retention we have never seen a single pylorus that was not fully patent. In one of these, however, there was some evidence of cicatrization as shown by an elliptical shaped pyloric orifice which had no apparent reduction in the area of the lumen. In some of these cases of retention the peristaltic waves were very shallow, or even absent. In the latter cases the pylorus did not close during the period of observation.

There is still another curious fact which has been observed on numerous occasions, particularly in reference to the use of the flexible gastroscope, but which has not been commented upon nor for which has any explanation been vouchsafed. In order to distend the walls of the stomach so that a

view of them can be obtained, air is pumped into the stomach. This is done by means of a small hand bulb similar to that used in connection with the sigmoidoscope. In a normal stomach the air stays in place once the proper degree of distention has been obtained and none has to be added during the course of the examination. However, in stomachs in which a gastroenterostomy has been performed the air leaks out, particularly at the beginning of the examination, and has to be replaced constantly. The air must escape into the jejunum for it does not come out of the cardia and esophagus. This indicates that there is some mechanism in the duodenum which prevents the passage of air from the stomach through the pylorus, which we have already noted is open practically all of the time.

Thomas and Morgan have noted that as a peristaltic wave approaches the pylorus there is a marked inhibition of the rhythmic contractions of the first part of the duodenum, and that recovery of the normal tone and peristaltic activity of the duodenum takes place when the pylorus closes. Could it not be a fact that the tone of the duodenum varies? That when the stomach is ready to eject material into the duodenum, its tone diminishes so that it can dilate sufficiently to conform with the bulk of this ejected material? Between these periods the tone is so increased as to be able to withstand the usual slight variations of pressure within the stomach due to peristalsis. This apparent contraction of the walls of the duodenum is what keeps the air within the stomach during the gastroscopic examination. In the case of the stomach with the gastroenterostomy opening, the jejunum has none of these qualities of increased and decreased tone and so there is no barrier to the passage of air into and along its lumen. Of course there is a limit to the volume of air that can be forced into the jejunum at the mild pressure used in inflating the stomach, and after this volume has been reached the back pressure equals the pressure within the stomach and no further leakage occurs.

From these foregoing observations we have deduced that there must be some very definite mechanism not previously described that enables the stomach to empty itself. This mechanism must be different from what has been described heretofore, for these facts seem very evident and positive, and they do not fit exactly into any previous explanation. It can be argued that a stomach filled with air or with the usual barium meal does not behave in the same fashion as one filled with the usual types of food. This is true, but it is also true that these facts have been observed with very great regularity, signifying to us that there must be some underlying mechanism which is very definitely established and which must serve some function. The following is a theory based upon these observations.

The stomach is divided into three portions: the antrum, the body and the fundus. The antrum is that portion which lies distal to the *incisura angularis* and the *musculus sphincter antri;* the body is the remaining portion except for that part which is above the cardia which is called the fundus. This latter portion contains the air bubble. When empty the walls of the

stomach lie in close apposition. This approximation of the walls must be forceful at times, for we have noted in certain individuals that the barium meal collects for a time in the fundus and that gradually a trickle of it filters down through the body to the antrum. This apparent spasm persists over a considerable period at times. Normally, however, the walls of the stomach enlarge enough to accommodate the amount of material that is placed inside of it and there is not any increase in pressure within the stomach due to stretching or contraction of the walls. When filled with food the body of the stomach acts as a reservoir, in which the food is retained and gently mixed and agitated by the shallow peristaltic waves which start in its upper portion and progress in a caudad direction. If the stomach is carefully observed over a considerable period, waves can be seen going in an opposite direction. These are apparently normal according to Alvarez. Here the hydrochloric acid and other juices are mixed with the food and some of the changes take place which prepare the ingested material for future digestion. Other factors probably help in this mixing process: the musculature of the abdominal wall for one. Normally these muscles are contracting and relaxing frequently, which in turn must exert some alternating pressure and relaxation upon the filled stomach. The movements of respiration, that is contraction and relaxation of the diaphragm and the accessory movements of the abdominal muscles must affect the stomach as well. All these factors assist in bringing the contents of the body down to the antral region.

When the food material is in the antrum it is further kneaded by the far more powerful contraction waves found here. Probably certain currents are set up which bring the food best prepared at the time to the region of the pylorus. When the duodenum is ready to receive some of the contents of the stomach, or when the contents of the stomach are in the proper state for passage to the duodenum, or when both of these factors are favorable, there is a contraction of the *musculus sphincter antri* which divides the stomach into two distinct compartments. This contraction must of necessity involve a fairly large mass of muscle which shortens the antrum and when the closure is complete raises the hydrostatic pressure of the antral contents. There is also at this time what might be termed a systole of the antrum; that is, the muscle of the antrum contracts and exerts still more hydrostatic pressure. As we have stated, the pylorus is open at practically all times. It being open, and the junction of the body and antrum of the stomach closed, the liquid food is literally squirted into the duodenum and cap under considerable pressure. That this is probably true is evident when we remember how rapidly, under the fluoroscope, the barium mixture enters the duodenum and how far it travels before reaching a stop. Shortly after this so-called systole starts, the usual contraction wave starts just distal to the *musculus sphincter antri.* This wave is probably no deeper than usual, but appears to be so because the antrum is in a hypertonic state. Once the wave starts the constriction of the *musculus* begins to relax; but the flow of the liquid is already under way and much of the duodenum is filled, so that the

wave tends to keep the current of the liquid going in the same direction, even though the pressure from the systole is relieved. The principal work has been done by the systole, and the contraction wave keeps going what was already set in motion. When the wave arrives at the sphincter, the pylorus closes and reflux is prevented. Apparently the only function of the pylorus is to prevent reflux.

The cap and the duodenum are filled under a certain amount of positive pressure, and the cap acts as a pressure regulator. Its musculature is thinner than the rest of the duodenum and it has more expansile qualities. It is filled with the first rush of liquid, expands to its limit, thereby taking up the momentary excess of liquid and acts as a reservoir. With the closure of the pylorus the cap tends to partially empty itself, passing on its contents to the duodenum. In this way we have a mechanism which tends to keep a constant pressure within the duodenum, so that this portion of the gastrointestinal tract is not subject to variation in pressure that would be present if the stomach contents were ejected suddenly into it. This function might be compared to the expansile qualities of the aorta, which by expanding with each systole of the heart, tends to equalize the pressure in the systemic circulation. When the pylorus again opens the hydraulic pressures within the stomach and duodenum are equalized, and when the duodenum is again ready to receive more material the process is repeated.

We have postulated that there is a variation in the tone and peristalsis in the duodenum. When the duodenum is ready to receive some of the stomach contents its tone decreases and its peristalsis is slowed up. This is probably coincidental with the initiation of the systole of the antrum. When the systole is completed the tone is raised in the first portion of the duodenum, the walls are in apposition again and cannot be parted by the usual pressures within the stomach. This produces an effective division between the duodenum and the antrum and prevents an appreciable exchange of material between the two until the duodenum is again ready to receive more food.

This whole course of events is particularly applicable during the earlier part of gastric digestion, when the stomach is more or less completely filled. Insomuch as the pylorus remains open practically all of the time there must be some slight exchange of contents between these systolic cycles. We do not claim that there is only one way in which food gets from the stomach to the duodenum. The usual peristaltic waves probably convey some material into the duodenum, particularly during the latter part of the time when the stomach contains food. Also there is a reflux of small quantities of material from the duodenum, especially at the end of the gastric digestive period. How the impulse is initiated by the duodenum when it is ready to receive more food, is difficult to determine and does not really concern us in this paper. It may be merely a matter of differences in pressure; when the duodenum is empty, when the pressure is lower than it is in the stomach,

the systole is instigated. It is not a matter of acidity and alkalinity for it has been observed many times that a stomach, in which there was no demonstrable acid, emptied just as well as one which was normal in this respect.

The reason for gastric retention—why some stomachs are slow in emptying or do not empty themselves entirely—requires an explanation. As we have said, at no time have we ever seen a pylorus that was not patent. We have never seen anything that suggested a spasm or a cicatricial closure. The reason for non-emptying must lie in mechanisms not as simple as mere stenosis. Certain types of retention might be explained upon the basis of atonic musculature of the stomach wall: that the musculature did not have enough tone to produce an actual systole, and that whatever emptying occurred was due to the usual antral peristalsis. This would indeed slow the process up considerably, if not actually prevent it. In other types of retention the difficulty may lie on the duodenal side of the pylorus. It is being recognized that duodenitis is a more common condition than was previously suspected. If a duodenum was acutely inflamed, its normal gradient would be disturbed and raised. This could delay or interfere with the emptying of the duodenum and therefore delay its preparation for the reception of stomach contents. Then again perhaps there might be some functional disturbance of the variations in tone of the first portion of the duodenum, so that the general tone was raised and during the relaxed phase, the relaxation was not complete enough to allow much food to enter during systole. Or perhaps the intervals between the relaxed phases are increased in duration and the systolic phase in the antrum occurs with decreased frequency. In all events there are probably a number of different reasons for gastric retention. Clinically we know that some types clear up with rest in bed and adequate medical treatment but tend to recur, and that other varieties do not improve under this regime and surgery has to be resorted to in order to effect a cure.

We present this theory, knowing full well that the chain of evidence lacks many links. The direct experimental proof of such a theory would require apparatus of greater delicacy than is now available, as well as development of special technics. For instance, to prove that during the systolic period of the antrum there was an increase in hydraulic pressure in this part as compared with the body of the stomach would require something far more delicate than the double balloon apparatus. The variations in pressure of necessity must be comparatively small, and the limits of error of such an apparatus are far too large to make it of any use.

In summary we present a theory to explain the course of events that takes place during the emptying of the stomach. This theory includes only the mechanics and hydrodynamics involved. The *musculus sphincter antri* contracts, forcibly dividing the stomach completely into two compartments. As this occurs there is an increase in tone of the antrum, which applies equal pressure upon its contents, forcing them through the pylorus under some

pressure. The usual peristaltic wave then passes over the antrum and when it reaches the pylorus and blends with it, the pylorus closes and remains so for only about one second. The first portion of the duodenum exhibits increased tone except during this cycle when the tone decreases.

BIBLIOGRAPHY

1. Wright, Samson: Applied physiology, 6th Ed., page 554.
2. Howell, William H.: Text book of physiology, 12th Ed., page 758.
3. Starling: Principles of human physiology, 6th Ed., page 579.
4. McLeod: Physiology in modern medicine, 8th Ed., page 665.
5. Alvarez, Walter: Mechanics of the digestive tract, 2nd Ed., 1928.
6. Best and Taylor: Physiological basis of medical practice, 2nd Ed., 1940.
7. Thomas and Morgan: A study of reflexes involving the pyloric sphincter and antrum, Am. Jr. Physiol., 1934, cviii, 683.
8. Cole, L. G.: Value of serial radiography in gastrointestinal diagnosis, Jr. Am. Med. Assoc., 1912, lix, 1947.
9. Eustermann and Balfour: Stomach and duodenum, 1st Ed., 1936.

THE PATHOLOGICAL PHYSIOLOGY OF THE EARLY MANIFESTATIONS OF LEFT VENTRICULAR FAILURE*

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William Harvey described and demonstrated the circulation of the blood in 1628, but long before there was any such adequate notion of the function or pathology of the heart the vital importance of this amazing organ was appreciated. This appreciation is attested by the position and significance of the word "heart" in the English language. The *heart* is the center of objects, the essence of ideas, and it is both the seat and the synonym of love and courage. Hearts may be warm, cold, empty, full, hard, or soft. Among other materials, they may be made of oak, stone, ice, or gold. Their behavior also is remarkable. Under appropriate circumstances they leap up, come up in the throat, or drop into one's boots. They may be worn upon the sleeve or set upon some object; they may be broken, melted, lifted up, or lost. They may even have wind around them.

Hearts also pump blood, and this essential function may be disturbed. When this occurs the result may be what is referred to as failure of the heart or failure of the circulation. I propose to discuss one isolated but important aspect of heart failure—the mechanisms by which failure of the left ventricle produces symptoms, signs and disability.

The left ventricle, or better, the left heart, is one of two pumps which make up the central mechanisms for moving blood. It receives blood which has passed through the lungs and propels it throughout the systemic arteries. Without entering upon a discussion of certain technical and controversial topics such as cardiac output, we may set up as a basis for our discussion certain accepted results of failure of the left ventricle. When the left heart fails the left ventricle dilates. This dilatation, for reasons which do not concern us here, is followed by an accumulation of blood in the left auricle and a rise in left auricular pressure. These changes, if the process continues, are succeeded by an increase in the volume of blood in the lungs and, unless there is a corresponding increase in the vascular bed, by a rise of pressure in the pulmonary veins, the capillaries and eventually the arteries.

There is nothing new or strange in this concept of left-sided heart failure. James Hope [1] described it clearly over a hundred years ago, in these words: "So long as the left ventricle is capable of propelling its contents, the corresponding auricle, being protected by its valve, remains secure. Hence, in a large majority of cases, the auricle is perfectly exempt from disease, while the ventricle is even enormously thickened and dilated. *But when the*

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*distending pressure of the blood preponderates over the power of the ventricle, its contents, from not being duly expelled, constitute an obstacle to the transmission of the auricular blood. Hence the auricle becomes overdistended, and the obstruction may be propagated backward through the lungs to the right side of the heart,** and there occasion the same series of phenomena. . . .

"The primary effect of universal obstruction of the lungs by engorgement is to produce edema of their cellular tissue and dyspnea; whether the latter depends solely on the engorgement or partly also on spasm of the bronchi excited by the irritation of that congestion is difficult positively to determine, though the latter is highly probable."

In recent years this general thesis has been restated and important new facts added by Weiss and Robb,[2] by Harrison and his colleagues,[3] by Paul White,[4] by Hitzig, King and Fishberg,[5] and by many others. In spite of this growing understanding and this informative literature there is still too little appreciation of certain matters of great moment to patients, viz.:

1. Pulmonary congestion due to left ventricular failure may occur in the absence of peripheral congestion.
2. Pulmonary congestion, by and large, is more dangerous to life and activity than peripheral congestion.
3. Many methods of examination give information only about the peripheral circulation (e.g., measurement of arterial and venous blood pressures) and tend to focus attention upon it, whereas there is in the pulmonary vascular system another set of pressures quite as important but at present inaccessible to measurement.
4. The severe symptoms due to such localized left-sided failure may respond well to treatment if their nature is understood.

The purpose of this paper then is to consider the results, in terms of symptoms and signs, of left ventricular failure leading to dilatation of the ventricle and the accumulation of blood and pressure in the left auricle and the pulmonary vascular system.

The manifestations of such congestion will be modified by many side factors. These side factors complicate the picture greatly, and mean that in different patients or in the same patient at different times a given degree of congestion may produce quite different results. Among these confusing factors are the following:

1. The total volume of blood in the body.
2. The volume of blood flowing into the lungs.
3. The amount and kind of plasma proteins.
4. The permeability of the pulmonary capillaries.
5. The number and availability of reserve capillaries.
6. The ability of vessels to withstand pressures tending to dilate them.

* The italics are mine. Author.

7. Many factors influencing the water balance of the body.
8. The sensitivity of various reflexes having their origin in the pulmonary and pulmonary vascular tissues.
9. The rate at which the accumulation takes place.

Accepting all these variables we may inspect some of the direct consequences of isolated left ventricle failure. They may be considered in two groups: those associated with the heart itself and those manifest in other parts of the body.

A. Manifestations associated with the heart itself.

1. The dilatation of the ventricle is usually demonstrable by roentgen-ray, and Weiss and Robb [2] were able to show that with this dilatation there is often a reduction in the excursion of the ventricle's shadow. This was true in patients who had little or no diminution in cardiac output.

2. *Pulsus alternans* appears to be associated with a change in function of the left ventricle which often precedes failure. When it occurs without tachycardia it should be interpreted as a warning signpost, suggesting left ventricle weakness and perhaps failure not far behind.

3. No arrhythmia is predominantly associated with left ventricular failure, but the onset of auricular fibrillation occurs not rarely in some relation to the development of left ventricular failure. When this occurs it is usually considered that the auricular fibrillation, by bringing about a rapid ventricular rate, is itself a precipitating cause of the failure. This is certainly so in some instances, but the cart and the horse may be turned around in others. It has been suggested by Brill and Meissner [6] that the distention of the left auricle resulting from left ventricular failure may be a factor in the *initiation* of auricular fibrillation. They point out that auricular fibrillation occurs most frequently in those conditions (mitral stenosis or failure of the left ventricle) in which the left auricular pressure is elevated. But most patients with left ventricular failure have a normal rhythm.

4. Left ventricular failure is frequently associated with a *gallop rhythm*, usually a mid- or protodiastolic type. It is usually considered that such a phenomenon is brought about by rapid ventricular filling, and that it thus may be a manifestation of an abnormally great difference in pressure as between auricle and ventricle.

Certain observations, recently made in my laboratory by Swank, Porter and Yeomans,[7] illuminate several aspects of the problems of failure of the left ventricle and may be presented here. These workers studied the effects upon certain circulatory functions of the intravenous infusion of fluid. They found, as others have done, that when saline solution, glucose solution, or blood were introduced in amounts which caused increase in the total blood volume of 50 per cent or more, many of the phenomena of congestive heart failure were reproduced. The phenomena so induced include dilatation of the heart, systolic murmurs, elevation of the venous pressures in lung and

in periphery, gallop rhythm, congestion of lungs and liver, and (in some animals) edema of the lungs. These phenomena occurred at a time when the cardiac output and the blood supply to the tissues were above the basal level. It may be debated (fruitlessly, I think) whether these animals had heart failure or not, but in any event the experiment permits us to study some phenomena often a part of what we call failure.

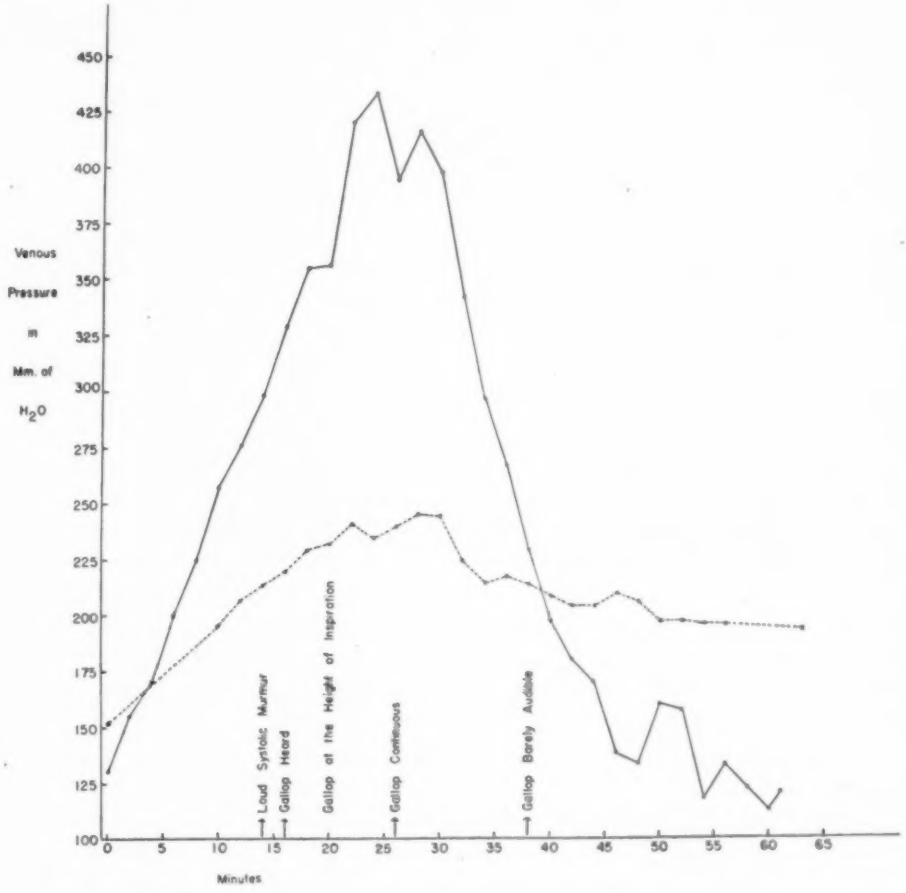

FIG. 1. The left auricular pressure (solid line) and the peripheral venous pressure (broken line) during infusion. The zero point of the manometers was at the level of the skin of the dog's back. The infusion was stopped after 30 minutes.

Figure 1 records the peripheral venous pressure and the left auricular pressure in a dog subjected to such an injection. This animal was anesthetized with alpha-chloralose. The injected fluid was normal saline and was put into a femoral vein at the rate of 2.7 c.c. per kilogram per minute for 30 minutes. Thus a 24 kg. dog received a total of 1944 c.c. in 30 minutes. There is a rise in the venous pressure of both circuits beginning immediately

after the onset of the injection; the pulmonary venous pressure rises more rapidly, in this animal, than the peripheral and reaches a maximum height of 433 mm., while the systemic venous pressure goes only to 240 mm. After cessation of injection the pressure falls rapidly in both circuits and within 15 minutes is approaching normal. The interest of this chart is that during the injection certain new signs appeared. When the left auricular pressure reached 329 mm. of water a gallop rhythm was heard; when the pressure had fallen to 198 mm. it was no longer audible. A systolic murmur also came and went with a series of events which may have been expected to dilate the mitral ring.

Further evidence that the basis of gallop rhythm is to be found in an elevated auricular pressure is seen in some recent work of Stead and Ebert.[8] By trapping blood in three extremities they were able to diminish the effective blood volume by some 16 per cent. In a hypertensive subject the pooling of blood in the extremities was accompanied by a disappearance of the gallop, presumably because of a lowering of left auricular pressure. When the tourniquets were released the gallop returned.

These observations seem to associate gallop rhythm with a high pressure in the left auricle. In my judgment a gallop rhythm is a useful sign because it may be a relatively early indication of rising auricular pressure, and we are probably all tardy in our recognition of left ventricular failure.

These experiments also emphasize the highly significant fact that the degree of pulmonary congestion may alter with great rapidity.

5. Wood and Selzer,[9] working in the National Hospital for Diseases of the Heart and the British Postgraduate Medical School, have recently suggested what they think may be an electrocardiographic sign of left ventricular failure. In a recent communication they draw attention to a type of P-wave, which is wide and bifid and of low voltage, which they have found in association with left ventricular failure in hypertension and in aortic incompetence.

6. A large increase in the size of the roentgen-ray shadow of the left auricle is not frequent, according to the careful studies of Weiss and Robb.[2] The observation is in striking contrast to the situation in mitral stenosis, in which a marked enlargement of the left auricle's shadow is regularly observed. Most of the patients studied by Weiss and Robb had hypertension or aortic disease as the basis for their left ventricle failure. It is accepted, on the basis of wide experience, that auricular distention from mitral stenosis is of long duration as compared with that occasioned by left ventricular failure. Some recent work by Eppinger, Burwell and Gross[10] has shown that the great increase in pulmonary blood flow which may occur in patients with patent ductus arteriosus may be associated with a definite increase in size of the left auricle. It may be that even a normal mitral valve is not wide enough to transmit so great a volume of blood without an elevated auricular pressure, or this picture may be due to left ventricular failure of

long standing. However that may be, the left auricle is usually dilated when the ductus arteriosus is widely patent.

B. When we leave the heart itself and turn our attention to the pulmonary vascular bed we encounter manifestations at once more complex and more disquieting than those we have so far considered. We are greatly handicapped in the study of the pulmonary circulation by the lack of methods for measuring pressure in the pulmonary veins and arteries. These are no doubt as important as similar measurements in the systemic circulation but their variations are thought about much less, presumably because we cannot get precise information about them. Left ventricular failure results in an increase in the amount of blood in the lungs, as shown by many studies (Blumgart and Weiss,[11] Weiss and Robb [2]). This increase results in the diminution of air space, unless there are appropriate compensatory changes, in alterations in the consistence of lung tissue which tend to diminish its mobility, in a slowing of the movement of blood, in the opening up of new capillaries, and in an elevation of pressure in pulmonary vessels. These changes, through their mechanical and reflex effects, bring about a series of symptoms and signs, including:

1. Prolongation of the pulmonary circulation time
2. Diminution of vital capacity
3. Dyspnea (including the paroxysmal type)
4. Cough
5. Bronchial constriction
6. Roentgen-ray evidence of congestion
7. A loud pulmonary second sound
8. Edema (either interstitial or alveolar)
9. Hemoptysis } (these are late manifestations)
10. Cyanosis }
11. Laryngeal paralysis?
12. Pleural effusion?

None of these manifestations is simply produced, their mechanisms are complex, and they may interact with each other to complicate matters still further. Each of them, however, may be explained primarily on the basis of accumulation of blood and pressure in the pulmonary vessels. A few examples will suffice.

1. Dyspnea, in general, as Peabody [12] showed, occurs when the actual volume of ventilation exceeds a certain (or individually uncertain) fraction of the maximum ventilation possible. Dyspnea is encouraged, therefore, by factors which either increase the ventilation or decrease the maximum ventilation possible. Harrison [3] has illustrated the links in the chain of events leading from left ventricular failure to dyspnea, and to its paroxysmal exacerbation in an attack of cardiac asthma. It is easy to see how left ven-

tricular failure reduces the maximum ventilation, since the vital capacity is reduced by the space-occupying extra blood in the lungs, by the stiffening effect of congestion on the lung tissue, and (in some patients) by interstitial or alveolar edema. Bronchial constriction also may occur to limit ventilation. At the same time the congested lungs are the source of vigorous reflex stimulation of respiration, as was shown by Harrison [3] and by Churchill and Cope.[13] Similar reflexes may be important in cough and in bronchial narrowing. It is important to remember that severe dyspnea and cardiac asthma can occur in the absence of any demonstrable edema, i.e., in the absence of râles.

Is dyspnea to be called an *early* symptom of failure of the left ventricle? It certainly is, and not very rarely the first symptom of which the patient gives an account is an attack of paroxysmal dyspnea, most often coming on at night. True, the more careful the history and the more sensitive and observant the patient the more frequently one will obtain an *earlier* history of dyspnea with exertion, but there are patients in whom severe attacks come early in failure. The observations in dogs just presented show how pulmonary congestion may occur with great rapidity if the capacity of the left heart is overtaxed.

Dyspnea is not only an early symptom of left ventricular failure; in some ways it is the key symptom. It may be dyspnea on exertion, nocturnal paroxysmal dyspnea, periodic respiration, orthopnea, or continuous dyspnea. Its severity and type are modified by many influences: the excitability of the nervous system, the chemistry of blood and tissues, the mobility of diaphragm and ribs, the size of the dead space and the metabolic rate. But the *fundamental* mechanism of dyspnea in left ventricle failure is congestion of the pulmonary vascular systems.

2. Cough is important, because it is not only an early symptom but also a form of physical work which may lead to further pulmonary congestion. Its causation is complex and it is often influenced by extracardiac factors.

3. Edema, hemoptysis, and cyanosis are on the whole late rather than early results of left ventricular failure and need only to be mentioned, although there are plenty of interesting and unsolved problems connected with them.

4. Then there are certain signs the mechanism of which is not well understood. King, Hitzig and Fishberg [14] have reported three cases of recurrent laryngeal paralysis in left ventricular failure; this they ascribe to compression of the nerve by dilatation of the pulmonary artery. There is an obvious parallelism with the laryngeal symptoms of severe mitral stenosis, but the case is not clear. I am puzzled also by the relation of left-sided heart failure to pleural effusion; indeed, the whole question of the mechanism responsible for pleural effusion seems to me to need investigation.

At various points in this discussion we have touched on the similarity of the congestive phenomena of left ventricle failure to those of mitral

stenosis. In my opinion it is desirable to try to differentiate between the congestion due to unchanging mechanical obstruction (as in mitral stenosis) and those due to fluctuations in the working capacity of the myocardium, as in left ventricular failure. The utility of such a differentiation is, of course, to be found in the different reactions to treatment of the two groups, and in the differences in course and prognosis. In the case of a permanent and unvarying obstruction, such as mitral stenosis without myocardial failure, changes in the degree of pulmonary congestion are occasioned chiefly by variations in the amount of blood flowing into the lungs. When the obstacle is a failing ventricle there are two variables: the amount of blood flowing into the lungs and the severity of the interference with ventricular function. This double mechanism may explain the fact that rapid fluctuations in the degree of pulmonary congestion are much more frequent in patients with left ventricle failure than in those with mitral obstruction. Obviously the management of failure of the left ventricle requires measures to diminish the amount of blood flowing into the lungs and measures to increase the ability of the left ventricle for effective and economical work.

In conclusion I shall mention only three points for emphasis:

1. Left ventricular failure is frequent and dangerous, and in its early stages is often pure (i.e., without associated failure of the right ventricle). These early stages are apt to be seen in office or out-patient department rather than in wards.

2. The diagnosis of heart failure does not require high systemic venous pressure, an enlarged liver or peripheral edema. It may be made on the evidence of isolated failure of the left ventricle. Early evidences of such failure include: gallop rhythm, diminished vital capacity, prolonged pulmonary circulation time, roentgen-ray evidence of pulmonary congestion, and sundry varieties of dyspnea.

3. Our knowledge of left ventricular failure would profit greatly by the invention of a method of measuring the pulmonary arterial and venous pressures in patients by a painless, precise, and non-perilous procedure.

BIBLIOGRAPHY

1. Hope, James: A treatise on the diseases of the heart and great vessels, 1846, Philadelphia.
2. Weiss, S., and Robb, G. P.: Cardiac asthma (paroxysmal cardiac dyspnea) and syndrome of left ventricular failure, Jr. Am. Med. Assoc., 1933, c, 1841.
3. Harrison, T. R.: Failure of the circulation, 1939, Williams and Wilkins Co., Baltimore.
4. White, P. D.: Weakness and failure of the left ventricle without failure of the right ventricle, Jr. Am. Med. Assoc., 1933, c, 1993.
5. Hitzig, W. M., King, F. H., and Fishberg, A. M.: Circulation time in failure of the left side of the heart, Arch. Int. Med., 1935, lv, 112.
6. Brill, I. C., and Meissner, W. A.: The rôle of coronary artery disease in the etiology of auricular fibrillation, Ann. Int. Med., 1941, xiv, 1341.
7. Yeomans, A., Porter, R. R., and Swank, R. L.: Observations on certain manifestations of circulatory congestion produced in dogs by rapid infusion. B. Results in normal dogs, To be published.

8. Stead, E. A., Jr., and Ebert, R. V.: The action of paredrinol after induction of hemorrhage and circulatory collapse, Am. Jr. Med. Sci., 1941, cci, 396.
9. Wood, P., and Selzer, A.: A new sign of left ventricular failure, Brit. Heart Jr., 1939, i, 81.
10. Eppinger, E. C., Burwell, C. S., and Gross, R. E.: The effects of the patent ductus arteriosus on the circulation, Jr. Clin. Invest., 1941, xx, 127.
11. Blumgart, H. L., and Weiss, S.: The pulmonary circulation time, the velocity of venous blood flow to the heart, and related aspects of the circulation in patients with cardiovascular disease, Jr. Clin. Invest., 1928, v, 343.
12. Peabody, F. W.: Cardiac dyspnea, The Harvey Lectures, Series 12, 1916–1917, p. 248.
13. Churchill, E. D., and Cope, O.: The rapid shallow breathing resulting from pulmonary congestion and edema, Jr. Exper. Med., 1929, xlix, 531.
14. King, F. H., Hitzig, W. M., and Fishberg, A. M.: Recurrent laryngeal paralysis in left ventricular failure, Am. Jr. Med. Sci., 1934, clxxxviii, 691.

THE CRUVEILHIER–BAUMGARTEN SYNDROME; REVIEW OF THE LITERATURE AND REPORT OF TWO ADDITIONAL CASES *

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Introduction

In 1833 Pegot [1] observed a patient who presented the phenomena of dilated veins in the abdominal wall, with a caput Medusae and a loud venous murmur at the umbilicus. At necropsy a widely patent umbilical vein, a small but apparently grossly normal liver, and a large spleen were found. The details of this case were published and elaborated by Cruveilhier.[2] He believed that the patient was probably suffering from a congenital defect of the umbilical circulation, with atrophy of the liver, probably secondary to this defect. In 1908, Baumgarten [3] reported the case of a 16 year old boy who had distended abdominal veins, ascites, splenomegaly, anemia, and leukopenia. Death followed a gastric hemorrhage, and necropsy revealed a widely patent umbilical vein, splenomegaly " not of the Banti type," and an atrophic liver with subcapsular increase in fibrous tissue. Microscopically the hepatic lobules were small but otherwise normal, with only scattered increase in interlobular connective tissue. Baumgarten emphasized the absence of a well-developed cirrhosis and the patency of the umbilical vein itself, as essential features of the disease. He believed that the disease was based on hypoplasia of the liver, probably congenital in origin, associated with patency of the umbilical vein and venous stasis in the spleen.

A number of similar cases, usually designated " Baumgarten's cirrhosis," have been reported in the foreign literature since 1908. In 1922 Hanganutz [4] introduced the name " Cruveilhier-Baumgarten cirrhosis " which has been generally used by authors of subsequent case reports and theses [5] on the subject.

Our interest in this subject was aroused by the clinical study of two patients, one also at necropsy, showing many features of the disease as originally described by Cruveilhier and Baumgarten. In both instances, antemortem diagnosis of Cruveilhier-Baumgarten syndrome was made by members of the hospital attending staff.

No direct reference by name to the Cruveilhier-Baumgarten syndrome appears in the English literature, although cases described by Thayer,[6]

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Henry,[7] Wollaeger and Keith,[8] include features suggestive of this disorder. Moschkowitz,[9] and Johnson,[10] refer indirectly to the disease in papers on Banti's disease and allied disorders. Because of the lack of accurate description of this syndrome in the English literature, we have reviewed the cases reported under the name Cruveilhier-Baumgarten disease, as well as the cases otherwise designated by various authors, in order to establish the existence and nature of the disease, if possible. The original case reports, as well as the several theses that have appeared on the subject in the foreign literature,[5, 9] were consulted whenever available. Analysis of the various cases thus reported shows that considerable deviation exists from the clinicopathologic picture first described by Cruveilhier and Baumgarten. We have, therefore, listed all pertinent etiological, clinical and pathological data available in the various case reports, and shall attempt to summarize and analyze them in the light of the original descriptions. We were able to find 52 previously reported cases which are summarized in table 1. To these we have added our two cases, and an additional case found in the autopsy protocols of the Los Angeles County Hospital, which is included in table 1 as case 53.

Case Reports

Case 1 (number 54 in table 1). L. A., a Spanish female, aged 41, housewife, was first admitted to the Los Angeles County Hospital May 22, 1937, complaining of sudden onset of nausea, accompanied by vomiting of blood in large amounts some seven hours previously. In March 1936, the patient noticed distended veins over the lower portion of the sternum and upper abdomen. These produced no symptoms and she did not consider them significant. Her entry to the hospital was precipitated by a sudden severe pain across the epigastrium, accompanied by weakness and vomiting of approximately two and one-half quarts of bright red blood and large clots.

Past History: At the age of 10, the patient was operated on for the repair of an "umbilical hernia." Hospital records are not available for more complete information, but she recalls no local vascular disturbance of the umbilicus at that time. She had drunk one glass of wine with her meals for years. She had a positive blood Wassermann reaction in 1928 which became negative following a "course of treatment." Inventory by systems was essentially normal.

Physical examination revealed a well-developed and well-nourished female, in acute distress, vomiting at intervals considerable quantities of bright red blood and clots. The blood pressure was 135 mm. Hg systolic and 90 mm. diastolic. There was an old, healed midline incision in the lower abdomen. Several large, dilated and tortuous veins were noticed between the umbilicus and the sternum, disappearing from view near the xiphoid process (figure 1). On auscultation, a loud, roaring, continuous murmur was heard at the xiphoid process and just superior and to the right of the umbilicus. Thrills were palpated in these areas. The spleen was readily palpable, extending to the level of the umbilicus. The liver was not palpable and no ascites was demonstrable. Physical examination was otherwise negative.

Laboratory Examination: The urine was essentially normal. The hemoglobin was 75 per cent, erythrocytes 3,600,000, and leukocytes 6,250 with 81 per cent neutrophiles. The platelets were normal. The reticulocytes were 13.7 per cent. Blood Wassermann and Kahn tests were positive. The fragility test showed initial hemolysis at 0.48, and complete at 0.40. The icterus index was 6.6 units. Plasma

fibrinogen was 229 mg. per 100 c.c. of blood plasma. The urea nitrogen was 10 mg. per cent. Roentgen-ray of the chest on May 26, 1937, was essentially normal.

Clinical Diagnosis: Cirrhosis of liver; portal hypertension and splenomegaly; bleeding esophageal varices; and syphilis.

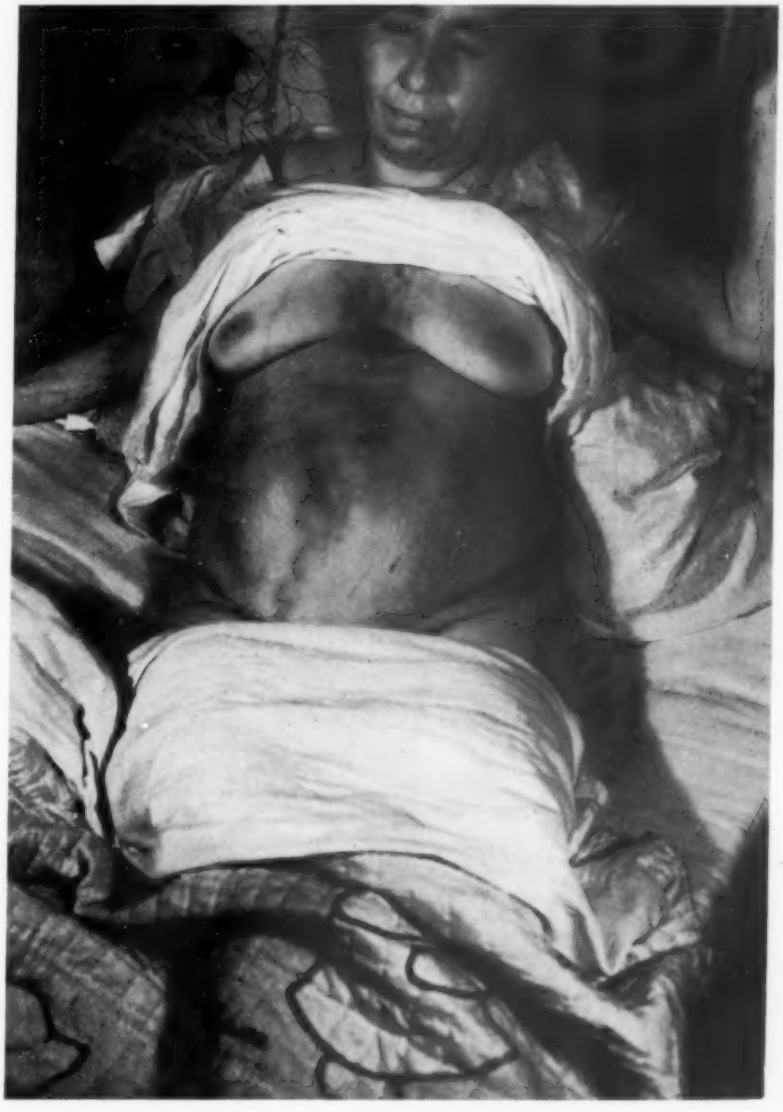

FIG. 1. Infra-red photograph of Case 1. Arrows indicate areas of loudest murmurs.

Course: In the hospital, the patient continued to have hematemesis from time to time, which decreased in amount and gradual improvement was noticed. On June 3, 1937, she was presented to the floor conference of the hospital medical department and the diagnosis of Cruveilhier-Baumgarten disease was suggested by Dr. V. R. Mason.

TABLE I

No.	Author—Date	Sex	Age	Etiol.*	Symptoms	Physical findings	Laboratory findings	Diagnosis
1	Pegot-Cruveilhier 1833–35	M	48	A T C	Abdominal pain following trauma in 1813; prominent veins in 1814 which increased in size during next 13 years. Gastric symptoms leading to death in 1833.	Dilated veins with a caput medusae. Slight murmur heard with stethoscope at umbilicus.		"Scirrhus" at pylorus.
2	Bamberger 1851					Thrill and murmur at sternum and umbilicus.		Cirrhosis.
3	Bouvillaud-LeMaire 1859	M	43	—		Murmur at sternum.		Cirrhosis.
4	Trousseau-Sappey 1859	F	50	—		Thrill and murmur heard over abdominal veins.		Cirrhosis.
5	Davies 1863					Epigastric murmur.		Hepatic cirrhosis.
6	Giaccomini 1873	F	22	—		Enlarged spleen. No murmur or thrill.		Cirrhosis.
7	Picchini 1890	M	16	—		Thrill and epigastric bruit.		Cirrhosis.
8	Bordoni 1890	—	41	M		Tremor and epigastric murmur 2 to 3 cm. above umbilicus. Enlarged liver and spleen. Caput medusae.		Cirrhosis.
9	Audry 1892	—	50	—		Continuous murmur over xiphoid and umbilicus. Enlargement of liver and jaundice.		Pneumonia.
10	Von Jaksch 1893	—	—	—		Epigastric venous sound. Liver and spleen enormous.		Cirrhosis.
11	Von Jaksch 1893	—	—	—		Left epigastric venous sound. Liver and spleen enormous.		Cirrhosis.
12	Rolleston	M	43	—		Epigastric murmur and devil's sound in neck.		Cirrhosis.
13	Piazza-Martini 1894	—	—	—		Slight low murmur on hepatic area especially in right arm pit differing from hepatic murmur. Epigastric venous sound in course of development of disease.		Cirrhosis. Syphilis (hereditary).
14	Taylor 1895	M	20	S	Swelling of abdomen with vomiting from age of 6. Hematemesis.	Epigastric venous sound in course of development of disease.		
15	Gambarati 1903	M	45	—		Venous hum with diastolic strengthening, located at the base of the xiphoid appendix, disappearing on constriction. Liver small, spleen enlarged; old pleurisy.		
16	Catti 1903	—	—	—		Thrill. Loud murmur characteristic venous murmur on tegmentous epigastric vein and to the left of it.		Cirrhosis with epigastric varicose veins.

*A, alcohol. S, syphilis. M, malaria. C, congenital. T, trauma.

TABLE I (*Continued*)

Cause of death	Liver	Portal system	Spleen	Miscellaneous	No.
	Gross: Small but normal. Micro: Not described.	Persistence and dilatation of umbilical vein.	Gross: Large and indurated; three times normal weight. Micro: Not described.	Benign obstructing lesion of pylorus.	1
		Patent umbilical or paraumbilical vein.			2
	Gross: 18 x 14 cm. in size. Micro: Cirrhosis.	Portal vein normal. Umbilical vein not examined.	Gross: 24 x 15 cm. only description. Micro: Not described.		3
		Paraumbilical vein discovered by Sappey.			4
				Not dead at time of report.	5
	Gross: Cirrhotic liver. Micro: Not described.	Dilatation of paraumbilical vein.			6
	Gross: Small liver. Micro: Not described.	Patent umbilical vein.	Gross: Large spleen only comment. Micro: Not described.		7
				Not dead at time of report.	8
				Not dead at time of report.	9
		Anomaly where coronary vein empties from ventricle (text obscure). No doubt that murmur originates from coronary vein of stomach.			10
		Splenic vein as large as little finger. Dilatation at all tributaries of portal vein, as well as those of epiploom and ligamentum teres. Slightly different from other venous sounds (murmur originated in splenic vein).			11
		Round ligament contains a closely crowded vein as thick as the little finger (paraumbilical.)			12
				Not dead at time of report.	13
	Gross: Liver cirrhotic. Micro: Not described.		Gross: Spleen enlarged. Micro: Not described.	No other anatomical investigation.	14
				No autopsy.	15
		Ligamentum teres very large and thickened. Subperitoneal veins. Passage of blood from small vessels into veins was noted.			16

TABLE I (*Continued*)

No.	Author—Date	Sex	Age	Etiol.	Symptoms	Physical findings	Laboratory findings	Diagnosis
17	Catti 1903	M	51	—		Marked venous sound at junction of xiphoid-sternum, increased by inhalation. No thrill. Spleen enlarged. Ascites present. Abdominal veins absent.		Atrophy cirrhosis.
18	Scheele 1904	M	45	—		Thrills in umbilical region and devil's sound increased by inhalation. Jaundice, dropsy and hepatomegaly.		
19	Baumgarten 1908	M	16	C	Swelling of abdomen with dilated abdominal veins; generalized weakness.	Ascites, splenomegaly, anemia and dilated abdominal veins. The absence of murmur and thrill is described.	R.B.C. 3.3 M. W.B.C. 2,600	Banti's disease.
20	Thayer 1911	M	49	A	Hematemesis for two years with right-sided abdominal pain.	Blanched. Pulse 100, regular and soft. Blowing precordial murmur. Liver palpable, spleen enlarged, abdomen full, veins distended. Loud continuous venous hum at xiphoid. Fever to 101.°	Hb. 30%. R.B.C. 3.4 M. Hb. 56%. W.B.C. 4,000. Hb. 75%. Urine negative.	Portal cirrhosis.
21	Masuda 1911	F	48	M prob.	Anemia and nephritis mentioned in history.		R.B.C. 1.8 M. W.B.C. 1,150.	Banti's disease. Chronic nephritis
22	Oetinger 1911	M	30	—	Vomiting of blood and slight jaundice. Melena.	No murmur or thrill. Spleen enlarged. Liver normal.	Urobilinuria	Banti's disease
23	Henry 1912	M	70	A	Fatigue dyspnea and swelling of ankles for 4 mos.	No thrills but continuous loud murmurs over ensiform. Prominent anastomosing veins over abdomen. No ascites. Liver not palpable. No edema.		Cirrhosis of liver.
24	Benque 1912	M	18	A?	Swelling of abdomen and lower extremities of 3 months' duration.	Ascites, large spleen, small and painless liver.	R.B.C. 4.0 M. Hb. 80%. W.B.C. 3,000. Wassermann negative.	Banti's disease.
25	Eppinger and Ranzi 1920	M	15	—	Epistaxis, melena, vomiting with hematemesis. Tuberculous peritonitis in childhood.	Liver hard and irregular, 4 fingers below the costal margin. Tremor over ectased veins between umbilicus and xiphoid process. Thrill present. Splenomegaly, anemia and peripheral edema.		Baumgarten's disease.

TABLE I (*Continued*)

Cause of death	Liver	Portal system	Spleen	Miscellaneous	No.
				Not dead at time of report.	17
				Not dead at time of report.	18
Hematemesis and thrombosis of epigastric veins following Talma operation	Gross: Liver greatly atrophied; 18 x 13 x 7 cm., particularly left lobe (length 7 cm.); capsule somewhat thickened; external surface irregularly coarse and knobby. At beginning of ligamentum falciform are "tied off knots of liver tissue." Cut surface shows increased connective tissue in region below capsule and some general coarseness. Micro: Considerable interlobular fibrosis in outer portions of liver coming down from capsule. Elsewhere, periportal tissue not thickened and "scarcely any connective tissue formation to be seen between acini. Acini small but otherwise normal."	Large patent umbilical vein communicating with epigastrics and vena porta filled with thrombus. Deep epigastric veins also thrombosed.	Gross: 26 x 13 cm. Greatly enlarged, with infarctions present. Micro: Not described.	Bone marrow gray-red in color.	19
Coma and convulsions.				No autopsy. Died in coma.	20
	Gross: Atrophic and slightly cirrhotic. Micro: Not described.	Patent and dilated umbilical vein with a caput medusae.	Gross: Enlarged spleen with phleboscleroses of splenic vein. Micro: Not described.	Circumscribed endophlebitis of vena cava and hepatic veins. Kidney showed chronic nephritis and heart was hypertrophied.	21
Died during splenectomy.	Gross: Liver cirrhotic. Micro: Not described.	Dilated epigastric veins and dilated "vein of round ligament." Dilated splenic vein.	Gross: Enlarged. Micro: Fibroadeni.		22
Pulmonary edema.	Gross: Small and granular liver. Micro: Not described.	Venous sinuses adhering to anterior edge of liver just below xiphoid cartilages. Xiphoid perforated by veins connecting reticulo-xiphoid sinus.	Gross: Lowered by adhesions. Micro: Not described.	Venous sounds originated in sinus and transmitted through blood vessels perforating ensiform.	23
	Gross: Weight 820 gm. Left lobe transformed into small connective tissue formation. Right lobe coarsely granular. Micro: Not described.	Patent umbilical vein communicating with internal iliac vein.	Gross: 1350 gm. Hypertrophied but hypertrophy due to stasis and not to fibroadeni. Micro: Enlarged sinuses very fibrous. Cell rich tissue seen in depths. "Not Banti's."		24
Hematemesis	Gross: Small and atrophic liver. Micro: Not described.	Umbilical and epigastric veins anastomose with marked dilatation.	Gross: Splenomegaly. Micro: Not described.	Pathogeny described as compression by tuberculous peritonitis or by cirrhosis.	25

TABLE I (*Continued*)

No.	Author—Date	Sex	Age	Etiol.	Symptoms	Physical findings	Laboratory findings	Diagnosis
26	Eppinger and Ranzi 1920	F	23	—	Distention of abdomen with edema. Increased thirst. Polyuria. Loss of weight.	Murmur and tremor synchronous with cardiac rhythm between umbilicus and xiphoid process. Liver and spleen enlarged. Ascites and edema present.		
27	Florand 1922	M	28	S A		Murmur and tremor palpated over two varicose lumps, one at the xiphoid and the other at the umbilicus. Edema, ascites and splenomegaly.		
28	Huber 1922	M	45	S A		Continuous systolic murmur and thrill from lower edge of venous tumor above and to the right of the umbilicus. Liver and spleen hypertrophied.		Cruveilhier Baumgarten's cirrhosis.
29	Hanganutz 1922	F	53	S A	Epigastric pain followed by distention and swelling.	Dilated vein between xiphoid and umbilicus 11 cm. long and size of little finger. Definite thrill at xiphoid. Atrophied right lobe of liver but large left lobe which was irregular and tender. Spleen hypertrophied.	Hb. 80%. Urine: Pus and hyaline casts. Wassermann positive.	Baumgarten's cirrhosis.
30	Akil Mouktar 1924	F	50	—		Venous murmur with intense thrill at base of xiphoid. Ascites and edema. Prominent abdominal veins.		
31	Popper 1924	M	43	M A	Lumbar pain and cough. Red and ulcerated skin. Eruption on legs. Dilated abdominal veins of unknown duration.	Dilated and tortuous thoraco-abdominal veins chiefly from xiphoid to umbilicus. Caput medusae around umbilicus. Blood flow away from umbilicus. Tremor and "mill-like" murmur in subxiphoid region. Large spleen.	Urine negative. Hb. 70%. R.B.C. 3.69 M. W.B.C. 5,400. Polys. 76%. Wassermann negative.	Cruveilhier Baumgarten's syndrome.
32	Bastai 1925	F	—	—				
33	Bastai 1925	F	—	—				
34	Visineano 1927	—	—	M		Murmur and thrill between ensiform and umbilicus. Small liver and hypertrophied spleen.		
35	Chabrol and Bernard 1928	—	—	—		Continuous murmur over dilated vein extending from saphenous vein to umbilicus.		
36	Gallavardin, Gravier and Puig 1928	—	—	—		Hollow spinning wheel sound at lower third of sternum. Hepatic cirrhosis.		

TABLE I (*Continued*)

Cause of death	Liver	Portal system	Spleen	Miscellaneous	No.
Generalized peritonitis.	Gross: Small and nodular cirrhotic liver. Micro: Not described.	Veins as large as the little finger were found in the round ligament connecting between the portal and epigastric veins.	Gross: 1000 gm. Capsule thickened. Perisplenitis. Micro: Pulp shrunken. Stroma not particularly increased.		26
	Gross: Cirrhotic, 1090 gm. 17 x 13 cm. Atrophy diffuse but predominantly right-sided. Micro: Periportal fibrosis with atrophy of liver cells and disorganized architecture.	Round ligament permeable from umbilicus to hilum of liver.	Gross: 2020 gm. 30 x 16 cm. with dense perisplenitis. Micro: Increased fibrous tissue.	Kidney revealed an adherent capsule and microscopically showed small glomeruli with swollen capsules, degeneration of tubular epithelium and some increased fibrosis.	27
				Not dead at time of report.	28
				Not dead at time of report.	29
	Gross: 1150 gm. with atrophy of right lobe and hypertrophy of left. Micro: Not described.	Right branch of portal vein smaller than left. Adhesive phlebitis at forking of two branches.			30
				Not dead at time of report.	31
	Gross: Surface of liver covered with reddish nodules varying in size. Micro: Portal vessels surrounded with connective tissue and in great measure occluded by recent thrombi. Biliary ducts filled with thick, transparent bile.	Great dilatation of portal vein with large recent thrombus in its principal branch to the hilus. No large supra-hepatic veins found. On right was a small sac which communicated with the lumen of the vena cava. No opening for the left branch was found. Umbilical vein was patent.	Gross: Dilated splenic vein. Thickened capsule. Micro: Not described.		32
	Gross: Enlarged and hard. Micro: Not described.	Branches and trunk of the portal vein appeared permeable. The round ligament was traversed by a central vein, the umbilical, which communicated with the left branch of the portal and anastomosed with the epigastrics. The openings of the supra-hepatic veins into the vena cava were like small, whitish tufts, resembling thrombi, the branch of the left lobe less restricted than the right.	Gross: Normal. Micro: Not described.		33
		Dilated paraumbilical vein. Two other veins near by.			34
				Not dead at time of report.	35
				Partial autopsy was negative.	36

TABLE I (*Continued*)

No.	Author—Date	Sex	Age	Etiol.	Symptoms	Physical findings	Laboratory findings	Diagnosis
37	Kaufman 1929	M	30	—		Thrill and murmur over flexuous vein leading from umbilicus to xiphoid appendix. Large liver and spleen. Edema of extremities but no ascites.		
38	Pagniezet and Rivoire 1929	M	34	M	Severe pain in right hypochondrium. Lassitude and asthenia.	Enlarged abdomen with no ascites. Liver normal. Spleen enlarged. No dilated veins. Loud murmur at xiphoid appendix. Thrill present.		Cruveilhier Baumgarten's cirrhosis.
39	Lupu and Gingold 1929	—	26	—		Continuous murmur and grinding sound stronger in systole noticed at ensiform umbilical area and another between the umbilicus and pubis. Dilated veins in umbilical xiphoid region. Liver and spleen large.	R.B.C. 1.8 M. W.B.C. 1,600.	
40	Brittana, Visineano and Solomon 1929	M	43	M	Lumbar, precordial pain and dry cough. Varicose veins of abdomen from birth. Loss of weight. Fever.	Enormous varicose veins between xiphoid and umbilicus. Murmur and thrill. Spleen palpated. Flow of blood from central region toward brain. Slight jaundice. Liver small. Ascites and edema present.	Hb. 80%. R.B.C. 3.8 M. W.B.C. 5,400. Wassermann negative.	Cruveilhier Baumgarten's disease. Aortic stenosis with insufficiency
41	Fiessinger and Michaux 1930	F	51	A	Digestive disturbance and jaundice at age of 18.	Abdominal distention. No ascites. Many veins, especially in umbilical region, with thrill and murmur to left of umbilicus. Liver and spleen large.	Wassermann negative.	Cruveilhier Baumgarten's disease.
42	Fiessinger and Michaux 1930	M	59	S M A	Hematemesis.	Abdomen distended with collateral circulation marked around umbilicus. Liver enlarged and firm. Spleen not palpated. Continuous murmur above umbilicus. No thrill. Recurrent ascites.	R.B.C. 1.4 M. Urine: bile and albumin. Rose Bengal 7.25.	Cirrhosis.
43	Quasch 1930	M	30	—	Epistaxis and vomiting.	Thrill and murmur over venous tumor at umbilicus for 10 years. Splenomegaly.		
44	Figuerido 1930	M	66	T	Severe blow in supraumbilical region. Abdominal pain and icterus. Progressive loss of weight and distention of abdomen.	Unilateral network of veins above umbilicus with murmur and thrill. Splenomegaly and icterus.	Blood sug.—63. Wassermann negative. W.B.C. 6,500.	Biliary cirrhosis.
45	Fontanel and R. Puig 1931	F	35	—	Digestive disturbances Oct., 1929; jaundice and oliguria Dec. 1929; distention of abdomen Jan. 1930; murmur at xiphoid March 1930.	Jaundice. Ascites. Collateral circulation not well developed. Liver small; spleen large.		Cruveilhier Baumgarten's disease.
46	Puig and Galibern 1933	M	40	A	Jaundice for 20 years with attacks lasting 2 weeks. Hematemesis 9 years.	Venous murmur along course of vein in midline below xiphoid. Thrill present; large, tender liver and enlarged spleen.	Wassermann negative. Fragility normal. W.B.C. 3,000. Polys. 68%.	Cruveilhier Baumgarten's disease.

TABLE I (*Continued*)

Cause of death	Liver	Portal system	Spleen	Miscellaneous	No.
				Not dead at time of report.	37
				Not dead at time of report.	38
				Not dead at time of report.	39
Cachexia Hyperthermia.	Gross: 1100 gm. Small and furrowed. Right lobe atrophied. Caudate lobe hypertrophied. Appearance and color normal; lobular markings obscured. Micro: Smallness of lobules and endophlebitis. Increased periportal fibrosis. Central veins showed slight sclerosis and intralobular capillaries were dilated. Diag.: Slight sclerosis without cirrhosis.	Practically entire absence of right branch of portal vein. Left branch large opening into "rest" canal which opened into paraumbilical vein. This continued to the abdominal wall running superiorly and then became superficial at the xiphoid in a venous chamber and anastomosed with the epigastric, internal mammary and subcutaneous thoracic veins.	Gross: 1200 gm. Patchy perisplenitis. On cut section follicles were not apparent. Micro: Rich in cellular elements. Malpighian corpuscles normal but splenic trabeculae hypertrophied. Diag: Stasis and chronic splenitis.	Heart showed aortic and mitral valvulitis. No varices in esophagus or rectum. Lungs revealed a chronic pleuritis with apical tuberculosis.	40
Hepatic insufficiency.				No autopsy. Died from hepatic insufficiency.	41
Coma.	Gross: 1450 gm. Annular cirrhosis. Micro: Not described.	Umbilical vein widely patent.	Gross: 140 gm. Micro: Corpuscles diminished in number and size.	Kidneys were normal.	42
				Not dead at time of report.	43
Fetid bronchitis.	Gross: 1300 gm. Irregularly granular. Micro: Ring shaped cirrhosis intense, especially in right lobe. No new formed bile ducts. Portal vessels dilated, few leukocytes. Marked granular swelling of liver cells.	Umbilical vein patent and equal in size to the portal vein in its two branches.	Gross: Enlarged three times. Micro: Not described.	Jaundice. Chronic pericarditis. Anatomical diagnosis of hepatic cirrhosis with patent umbilical vein.	44
Hepatic insufficiency, with coma.				No autopsy. Died of hepatic insufficiency.	45
	Gross: 1000 gm. Studded appearance typical of cirrhosis. Micro: Perilobular cirrhosis and inflammatory islands.	Umbilical vein permeable and dilated up to 2 cm. from the umbilicus where it anastomosed with paraumbilical veins.	Gross: 600 gm. Micro: Not described.		46

TABLE I (*Continued*)

No.	Author—Date	Sex	Age	Etiol.	Symptoms	Physical findings	Laboratory findings	Diagnosis
47	Spinelli and Pana 1934	M	16	—	Mild attacks of icterus.	Ascites, distended abdominal veins. Spleen not enlarged.		
48	Forns, Barcelo 1935	M	25	A	At age 18 a doctor noticed splenomegaly and dilated veins at epigastrium. Symptoms began at age 21 with pallor, asthenia and later hematemesis.	Souffle and continuous thrill over xiphoid; varicose mass of veins in paraumbilical region. Liver not palpable. Marked splenomegaly. Pallor and sub-icterus. At surgery, enormous spleen without adhesions, with vascular hilus and abdominal wall.	Urobilinuria. Hb. 70%. R.B.C. 3.0 M. W.B.C. 3,000. Polys. 72%. Platelets, 100,000. Wassermann negative.	Cruveilhier Baumgarten's disease.
49	Rossi and Anbrien 1935	F	50	—	Pains in right hypochondrium and epigastrium. Scanty urine, dark in color at times.	Distended veins over thorax and abdomen. Liver irregular and hard; just below costal margin. Spleen enlarged. No fluid.	R.B.C. 4.2 M. W.B.C. 7,400. Polys. 57%. Wassermann negative. Urine negative.	Cruveilhier Baumgarten's syndrome.
50	Lutembacher 1936	M	53	—	At age of 41 had a large liver with distended abdominal veins and diarrhea. 1935 developed ascites and edema of scrotum.	Distended abdomen with dilated abdominal veins. Continuous murmur below xiphoid of spinning wheel type with a perceptible thrill. Another mass of veins 10 cm. from umbilicus with murmur. Liver small. Spleen large and ascites present.	Urine negative. Wassermann negative.	
51	Guez 1936	M	32	—	Large dilated veins over abdomen for 9 years.	No murmur. Large liver, firm and smooth. No spleen or ascites.	Urine: Albumin.	Cruveilhier Baumgarten's disease.
52	Wollaeger and Keith 1938	M	38	—	Fever of 8 months' duration. Hematemesis in 1933 followed by jaundice and ascites. Omentopexy in 1933 and cirrhosis of the liver were noted at surgery.	In the region of the xiphoid there was a continuous harsh roaring murmur and palpable thrill. Dilated veins with a small liver and splenomegaly. High pulse pressure; capillary pulse and overactive heart.	Urine negative. Kahn negative. Hb. 11.6 gm. R.B.C. 3.3 M. W.B.C. 3,000. Urea 20. Total proteins 6.8. Albumin 3.4 Globulin 3.4.	1. Banti's syndrome with cirrhosis of liver. 2. Possible arteriovenous fistula.
53	Dodson 1930[1]	F	2	—	Jaundice for several weeks at birth; abdominal distention for several weeks before death.	Abdomen distended from ascites (1000 c.c. withdrawn); no murmurs or dilated abdominal veins described.	R.B.C. 3.9 M. W.B.C. 22,000. Cholesterol 152.	Cirrhosis of liver.
54	Authors' first case.	F	41	A?	Distended abdominal veins since 1936; hematemesis before entry to hospital.	Distended thoraco-abdominal veins; murmur and thrill at xiphoid and umbilical areas; palpable splenomegaly; liver not palpable.	R.B.C. 3.6 M. W.B.C. 6,200. Blood Wass. and Kahn positive. Icteric ind. 6. Urea N. 10.	Cruveilhier Baumgarten's syndrome.
55	Authors' second case	M	25	—	Abdominal swelling, 2 months.	Caput medusae with continuous thrill and murmur at umbilical area; ascites.	R.B.C. 4.2 M. W.B.C. 5,200. Icteric ind. 5.	Cruveilhier Baumgarten's disease

[1] Unpublished necropsy observation.

TABLE I (*Continued*)

Cause of death	Liver	Portal system	Spleen	Miscellaneous	No.
Died after omentopexy.	Gross: Chronic passive congestion of the liver. Micro: Not described.	Patent umbilical vein.		Old thrombosis of trunk of vena cava, suprahepatic, renal, spermatic and iliac veins. Abdominal and thoracic veins dilated.	47
Hematemesis	Gross: Small atrophic and granular, especially the left lobe. Micro: Not described.		Gross: Not described. Micro: Thickened trabeculae with fibroadeni.	Esophagus and stomach revealed no site for the source of the hemorrhage.	48
				Not dead at time of report.	49
Hematemesis.	Gross: Atrophic Laennec's cirrhosis. Micro: Showed cirrhosis without degeneration of uninvolved liver cells.	Umbilical vein not patent. Paraumbilicals large and dilated (1 cm.) flowing into the left portal vein.	Gross: Spleen large. Micro: Not described.	Kidneys, heart and aorta were normal.	50
				Not dead at time of report.	51
				Not dead at time of report.	52
Pneumococcic septicemia.	Gross: 460 grams, 15 x 10 x 9 cm. Broad scars and scattered nodules up to 2 cm. in diameter. Micro: Portal cirrhosis.	Umbilical vein widely patent.	Gross: 110 grams; firm. Micro: Severe chronic passive hyperemia.		53
Still alive.					54
Gastric hemorrhage.	Gross: 1300 grams; smooth; firm; fine periportal scarring with occasional tiny nodules. Micro: Atrophy and periportal fibrosis.	Umbilical vein widely patent.	Gross: 900 grams; firm with prominent trabeculae and obscured follicles. Micro: Increased connective tissue elements; dilated sinusoids.		55

The patient left the hospital August 18, 1937. She was not seen again until March 13, 1939, when she returned because of massive hematemesis of 24 hours' duration. With this admission she was acutely ill, quite pale, with blood pressure 115 mm. Hg systolic and 70 mm. diastolic. The spleen was enlarged and the abdominal murmurs and thrills were present as before. The blood count revealed hemoglobin of 48 per cent (Sahli), white blood cells 8,500 with 86 per cent polymorphonuclears. Blood transfusion was given, followed by slow improvement and cessation of bleeding. Additional laboratory findings before discharge were serum albumin 2.8 gm., cholesterol 185 mg. and cholesterol esters 134 mg. per 100 c.c. of blood.

With this last admission, splenectomy was tentatively suggested to the patient, but refused. She was then referred to the Out-Patient Clinic for observation and continuance of antiluetic therapy.

Case 2. J. S., a white American poultryman, aged 25 years, was admitted to the Los Angeles County Hospital January 28, 1938, complaining chiefly of swelling of his abdomen, of about two months' duration. He stated that he had been in good health until three years before, when he developed "kidney trouble," as evidenced by nocturia, low backache, and high blood pressure. At about this time, he noticed incidentally some swelling of the veins of the right side of the abdomen. Two months before entry, edema of the ankles, together with increasing ascites developed, necessitating paracentesis (7 liters); and he had two episodes of vomiting of small amounts of coffee-grounds material. He had also noticed failing vision for two weeks prior to entry.

Past history revealed no definite infections. He stated that he had consumed an average of a pint of whisky per month since the age of 14 years.

Physical examination revealed a somewhat emaciated white male in no acute distress. Temperature, pulse, and respirations were normal. The pupils reacted poorly to light and convergence. Ophthalmoscopic examination by Dr. Warren Wilson revealed pigmentary retinitis and papillitis. The lungs were clear. The heart was enlarged to the left and a soft, systolic murmur was heard at the apex. The blood pressure was 160 mm. Hg systolic and 90 mm. diastolic. The abdomen was markedly distended and numerous dilated and tortuous veins radiated from a caput medusae (figure 2). A soft, continuous murmur was heard just above and to the right of the umbilicus, where a thrill was felt. A definite fluid wave was present and the spleen was enlarged. The liver was not palpable. No other abnormalities were noted.

Laboratory: The urine was essentially normal except for moderately impaired concentration. Blood count revealed hemoglobin of 40 per cent (Sahli), erythrocytes 4,200,000, leukocytes 5,200 with 90 per cent polymorphonuclears. The Wassermann and Kahn reactions were negative. The non-protein nitrogen was 75 mg. per cent; creatinine 3.3 mg. per cent; icterus index 5 units; albumin 2.3 grams per cent; globulin 2.4 grams per cent. The electrocardiogram showed sinus tachycardia.

Course: On February 5, 1938, the patient was peritoneoscoped by Dr. John C. Ruddock, and 4,500 c.c. of clear, colorless fluid were removed. Atrophy, apparent fibrosis, and capsular thickening of the liver were noted externally, making biopsy impossible. The spleen was enlarged. It was also noted that there was a large, tortuous, dilated vein occupying the site of the ligamentum teres.

The patient's condition continued to grow worse, with several lapses of consciousness and convulsions during the week prior to his death. He died April 12, 1938, following a massive gastric hemorrhage. The clinical diagnosis was Cruveilhier-Baumgarten syndrome with gastric hemorrhage; chronic glomerulo-nephritis; and retinitis pigmentosa.

Necropsy * was performed 20 hours after death on an already embalmed body by one of us (L. J. T.) The following is a summary of the gross and microscopic findings.

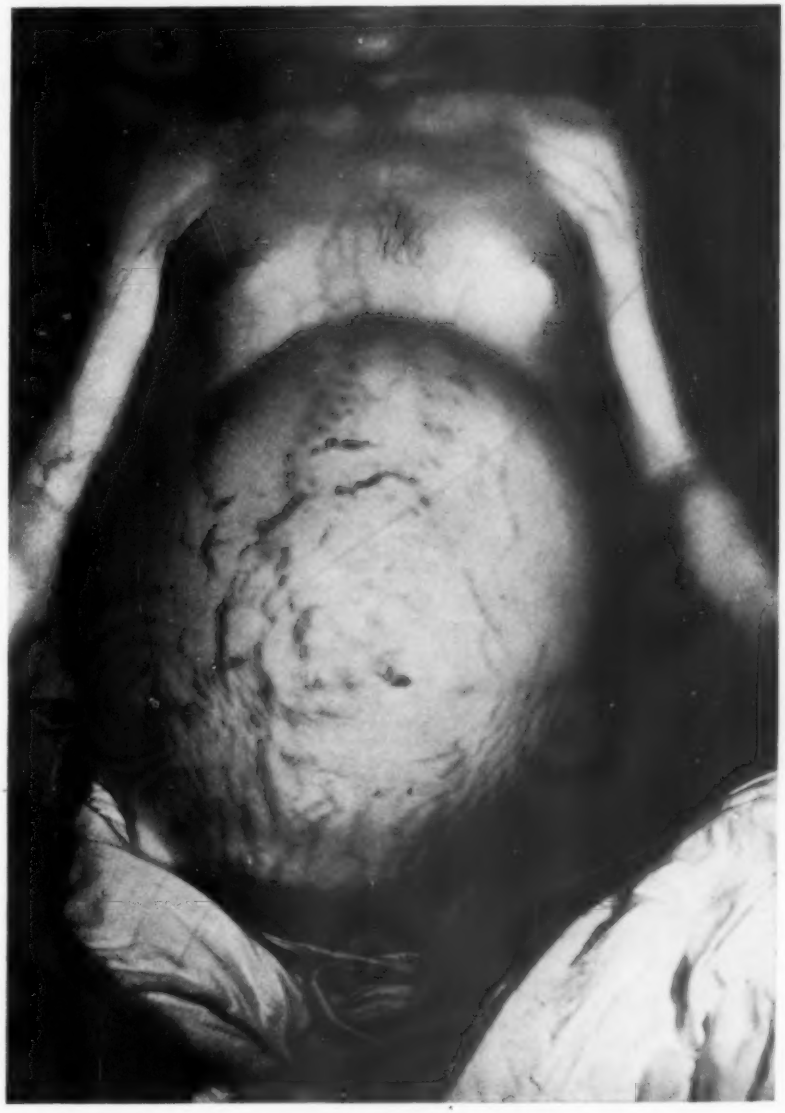

FIG. 2. Infra-red photograph of Case 2 showing caput medusae.

External Examination: Body is that of a fairly well developed but poorly nourished young white male. Abdominal distention and prominence of tortuous superficial veins over the abdomen are still evident, as well as the scars of paracentesis. Slight pitting

* We are greatly indebted to Dr. C. V. Atteberry for his interest in this case, and his aid in obtaining permission for autopsy.

edema of the lower extremities is present. Skull and central nervous system are not examined, and the neck organs appear normal in situ. The only abnormalities noted in the thorax are moderate hyperemia of the lungs with some bloody fluid in the bronchi and evident hypertrophy of the left ventricle which averaged 2 cm. in thickness. The weight of the heart is estimated to be 400 grams. The principal findings of interest were in the abdominal wall, digestive system, liver, and portal system. The abnormal veins found in the abdominal wall will be described largely in connection with the liver.

The peritoneal cavity contains about six liters of clear light amber fluid. All surfaces are smooth and glistening. The esophagus is dilated to about three times normal caliber throughout, particularly near the cardia. Some dilated veins are present along the outer wall of the esophagus, but no varices within the wall are noted. The cardiac sphincter appears normal. The stomach is dilated to at least twice normal capacity by a mixture of almost black liquid blood plus recent clots. The wall of the stomach is thin, the mucosa is smooth but marked by a number of pinhead hemorrhagic spots, none grossly certain to be erosions. The pylorus is normal. The small intestine is about average length and extreme edema is present throughout. On the mucosal surfaces of the jejunum, zones of edema involving the folds of mucosa produce the appearance of multiple polyps. In addition, in the terminal ileum, there are some areas of superficial erosion of the mucosa. Mesenteric veins surrounding these erosions are markedly dilated. The appendix is normal. The large bowel is moderately edematous, and in some areas the same polypoid edema noted in the mucosal folds of the small bowel is present. The pancreas is of average size, cut surface is firmer than normal, and the lobular markings are somewhat accentuated.

In the dissection of the abdominal wall, plexuses of veins both above and below the umbilicus are noted in the subcutaneous tissues, as well as in the recti muscles and sheaths. These veins lead toward the costal margin, the region of the xiphoid, and the femoral area. The largest are epigastric veins leading to the femoral veins. These veins, particularly the epigastric, communicate directly with an aneurysmal venous dilation, 6 cm. in diameter, situated just beneath the umbilicus (figure 3). From here a large vein replaces the ligamentum teres and runs in the edge of the falciform ligament to the liver. This is interpreted as a persistent and dilated patent umbilical vein. A somewhat smaller vein leads from the umbilical region toward a plexus of veins about the ensiform cartilage. The umbilical vein opens without difficulty into the left branch of the portal vein. As it traverses its fossa in the liver in a groove in the quadrate lobe, small branches can be seen going directly to the liver. Remnants of the ductus venosum lie in a ligamentous cord in the usual situation near the caudate lobe. This duct is only partially patent and when injected under pressure with colored liquid solution, its stenosed mouth in the inferior vena cava is indicated by staining of the wall without actual escape of the solution into the inferior vena cava.

The liver weighs 1300 grams and is smaller than normal, particularly in the vertical diameter. The average diameters are: transversely, 15 and 8 cm. for the right and left lobes respectively; vertically, 8 cm. for the right lobe; and anteroposteriorly, 15 cm. The quadrate lobe averages 6 cm. in transverse diameter; the caudate lobe, which is smaller than normal, measures 3 by 1.5 cm. The external surface of the liver is smooth, free of the diaphragm, and scattered telangiectatic venules are visible beneath the slightly thickened capsule. The liver cuts with increased resistance, exposing purple-gray to light brown surfaces. On closer inspection there appears to be accentuation of lobular markings by increase of fine fibrous periportal tissue without distinct nodular formation (figure 4). The gall-bladder is distended by thin bile; otherwise it is normal, as is the biliary tract.

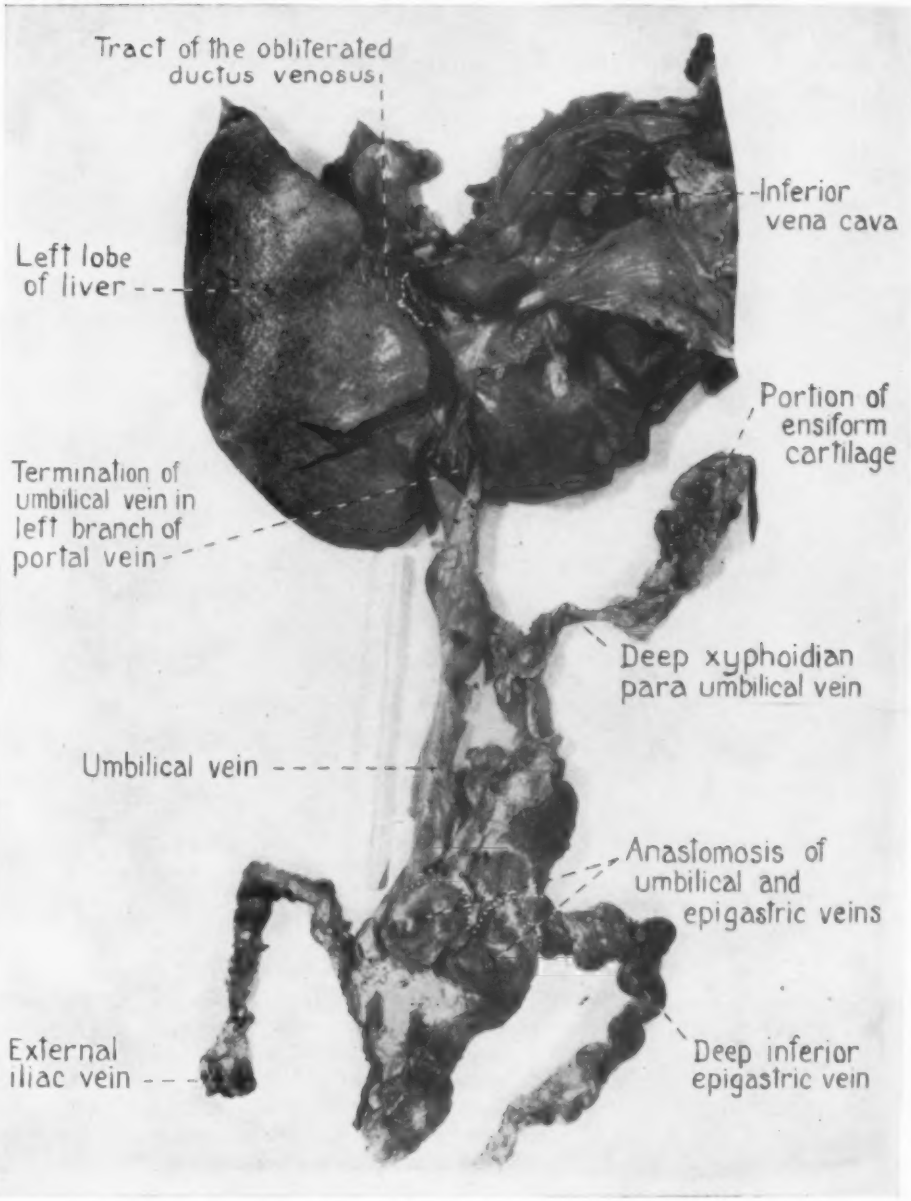

FIG. 3. Showing connections of patent umbilical vein with thoraco-abdominal veins and portal vein.

The total length of the inferior vena cava is 25 cm. with an average circumference of 3.5 cm. The mouths of the hepatic veins appear normal. In the superior group there are two veins, one from the right and left lobes respectively. In the inferior group there are five veins with slit-like openings. The branches of the hepatic veins appear normal as far as they can be traced. The portal vein is 7 cm.

in length, its average circumference is 3 cm. (normal 1.5 cm.), and its right and left main branches are 0.5 and 3 cm. respectively, each having an average circumference of 1.5 cm. The secondary branches are traced with some difficulty, the supporting connective tissue being noticeably thickened. The intima of the portal vein is smooth and occasionally slightly thickened. The umbilical vein is 23.5 cm. in length with an average diameter of 2 cm., and joins the left branch of the portal almost 3 cm. from the origin of the latter. All major tributaries of the portal vein are dilated to at least twice normal diameter. Occasional slight thickening without gross plaque formation is present in the intima of the splenic and superior mesenteric veins. These

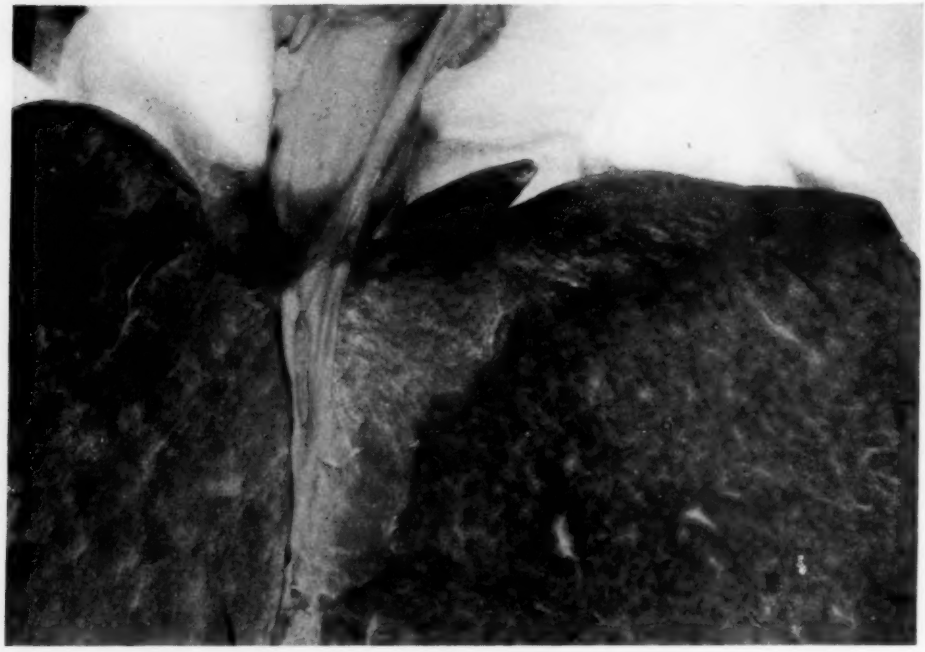

FIG. 4. Closer view of liver, external and cut surface, as well as the umbilical vein.

veins are widely patent throughout. The inferior mesenteric vein is also dilated and anastomotic channels can be seen to the hemorrhoidal veins. Collateral channels can be seen about the diaphragm extending toward the dilated azygos veins and similar dilated veins are present in the lienal pedicle. Dilated short gastric and coronary veins are present extending laterally toward the dilated esophageal veins previously described. Short gastric veins cannot be followed within the stomach wall. Several dilated venous channels are seen within the hepato-duodenal ligament, but do not approach the point of cavernomatous transformation.

The spleen weighs 900 grams and measures 26 by 13 by 5 cm. Its smooth thin capsule is free of adhesions to the diaphragm, but a few fatty tags are present carrying rather large dilated veins. Surfaces made by sectioning are firm, pale, with prominent trabeculae and veins, and obscured malpighian follicles (figure 5). It is interesting to note the tortuosity and early sclerosis without atheromatous plaque formation of the splenic *artery* near the hilus of the spleen. No generalized lymphadenopathy is present.

The kidneys are of equal size, similar appearance, and together weigh 200 grams. Capsule strips with difficulty from a coarsely granular surface mottled yellow-brown to gray. Cut surface is firm with cortex reduced to about 3 mm. in thickness and poorly demarcated from the medulla. Both are mottled yellow-brown to light gray with obscured markings. Vascular markings are rather prominent. Kidney pelves, ureters, and bladder are essentially normal. Prostate gland is of average size and is grossly normal.

The hypophysis was not examined. The thyroid and adrenal glands are grossly normal. Four parathyroid glands are found without difficulty, perhaps because of slight increase in size. A small fragment of thymic parenchyma is present in the fat pad.

Anatomical Diagnosis: Cirrhosis of liver, undetermined type and etiology, with patent umbilical vein (Cruveilhier-Baumgarten syndrome); chronic congestive splenomegaly; recent gastric hemorrhage; chronic glomerulonephritis; cardiac hypertrophy, hypertensive; phlebosclerosis, portal vein, slight; arteriosclerosis, local, splenic artery, slight; and dilatation of esophagus, type undetermined.

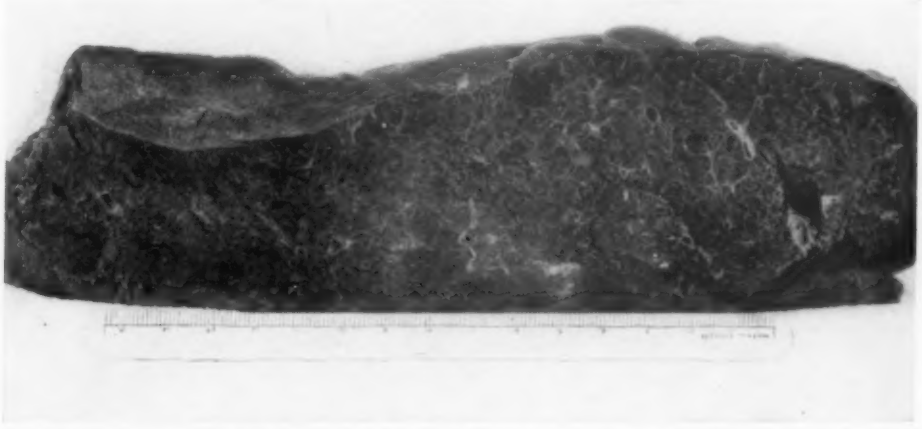

FIG. 5. Spleen, showing increase in fibrous tissue and prominence in venous markings.

Histological Examination: Liver—Blocks were taken to study the microscopic appearance of the liver throughout the various divisions of the portal and hepatic veins. Blocks were taken of both the left and right branches of the portal vein near the hilus, and show some thickening of the wall, particularly of the intima. An increased amount of loosely arranged connective tissue surrounds the vein, and scattered through it are a number of lymphocytes. The hepatic ducts and artery in the same area show no significant changes. Repeated sections to show the successive subdivisions of the portal vein show the persistence of a varying grade of periportal fibrosis. Generally, it is confined to the periportal area and does not appreciably deform lobular architecture (figures 6 and 7). Microscopically it consists of rather loosely arranged collagenous fibers in which there are scattered lymphocytes, plasma cells and histiocytes. Within this connective tissue there is apparent proliferation of bile ducts and apparent increase in vascular channels. The portal vein branches appear everywhere somewhat dilated with slight thickening of their walls. Serial sections made to follow the course of the fourth division portal branches show no great deformity in the histography of the liver and no recognizable hypoplasia of the portal radicles. There are varying degrees of intrusion of the thickened peri-

portal connective tissue within the lobule; usually this is slight. In some places, particularly near the second and third divisions of the portal vein, there is complete isolation of portions of one or more lobules by such extension of connective tissue, thus producing the appearance of nodules. Nowhere do these nodular areas appear to consist of newly proliferating liver cells. In sharp contrast to this periportal fibrosis is the almost complete absence of scarring about the tributaries of the hepatic veins as

FIG. 6. Liver at low magnification (× 15) to show periportal scars without gross deformity of architecture.

they are traced in various sections, beginning at the inferior vena cava. The interdigitations with the branches of the portal vein are fairly well preserved despite the fibrosis which is present. The liver cell cords are fairly well formed, most of the cells appearing smaller than normal and showing considerable fatty change, as well as cloudy swelling. Degenerative changes are also present in some of the nuclei. No bile staining is noted. The interlobular branches of the hepatic artery are prominent. With the Van Gieson stain the rather coarse periportal fibrosis is accentuated. The reticulum stain shows no particular changes within the liver lobules. Krajian stain reveals no spirochetes.

Umbilical vein—Sections were made from various portions of the wall and show a similar structure throughout. In most places differentiation into three coats is ill-defined. In the intima definite lining cells can be seen in some areas. Beneath these there is loosely arranged elastic and collagenous fibers. In the media the connective tissue is more firmly organized and scattered through it are fragmented smooth muscle fibers. This is confirmed in the Van Gieson stain. An edematous zone demarcates

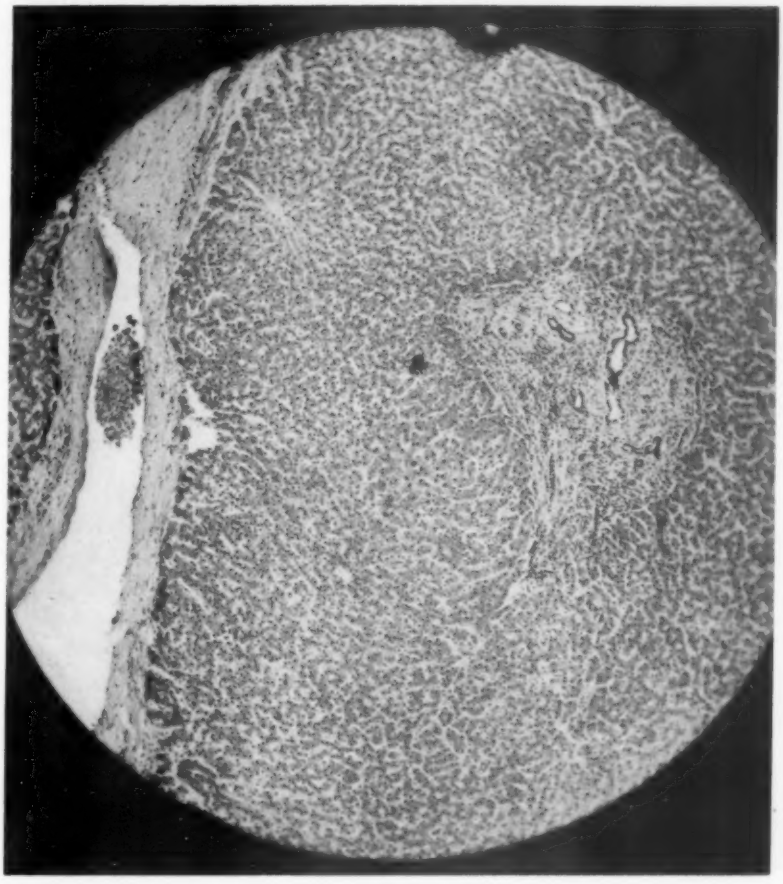

FIG. 7. Liver showing periportal fibrosis and absence of scarring about hepatic vein (× 60).

the adventitia which is thin and contains fine capillaries (figure 8). The histological appearance of the umbilical vein is similar to the normal control taken about the time of birth, showing early retrogressive changes, as described by Meyer.[11]

Abdominal wall in the region of the umbilicus—Sections show many dilated veins, usually with thickened intima and patchy phlebosclerosis. These vessels are no doubt collateral communications with the umbilical vein. Of interest is the occurrence of loose areolar tissue containing inflammatory cells very similar to that seen about the portal vein at the hilus of the liver.

Spleen—The capsule and trabeculae are greatly thickened. The large venous channels are dilated and have thickened walls and increased surrounding fibrous tissue. The

Malpighian bodies are decreased in number and size and are unevenly distributed. There is considerable periarterial fibrosis as well as scattered periarterial hemorrhage and siderofibrosis. General increase in reticulum cells and fibers is present with often apparent collagenous transformation of the stroma. The pulp is relatively acellular

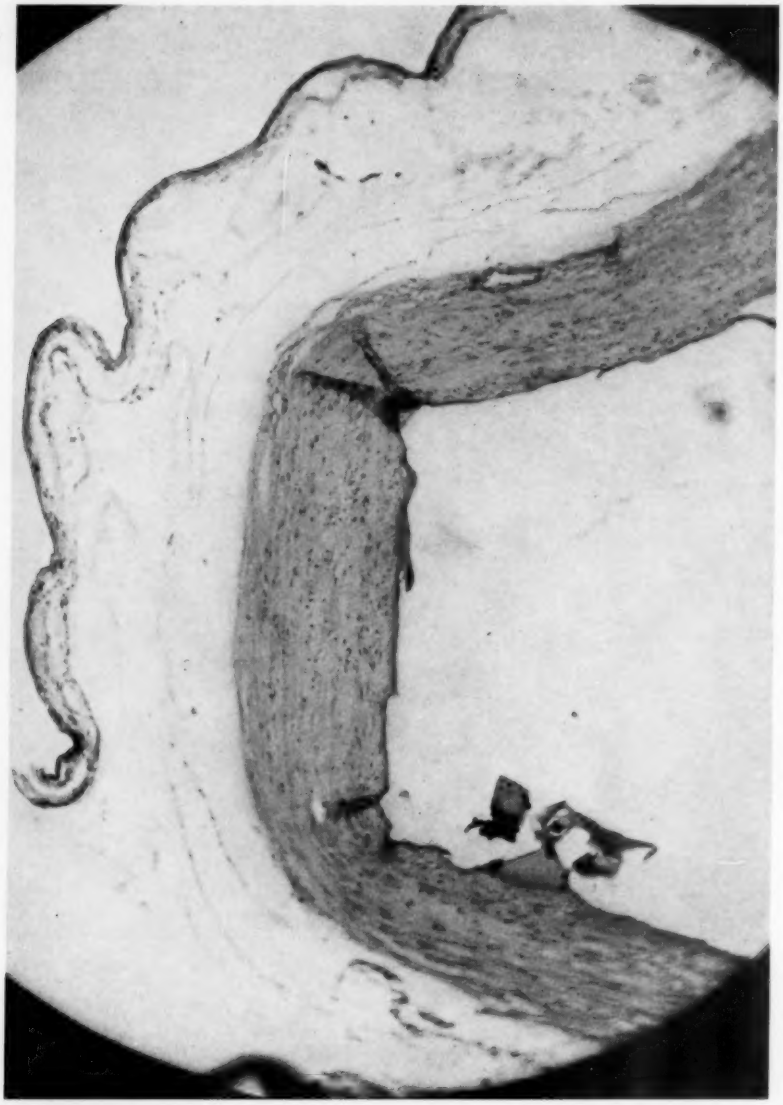

FIG. 8. Umbilical vein × 95. (Some retained injection material is present in the lumen.)

with increase in connective tissue elements. The sinusoids are numerous, distended, and have prominent linings. Sections of the splenic vein in the grossly slightly thickened areas show small phlebosclerotic plaques in the intima.

The *gall-bladder* shows postmortem change only. In the pancreas a general moderate increase in interlobular connective tissue with occasional fine intralobular ex-

tensions is noted. The tributaries of the portal vein are prominent with some thickening of their walls. No other significant changes noted. The mucosa of the *small intestine* is edematous and loosely infiltrated by polymorphonuclear leukocytes. The submucosa is markedly thickened by loose edematous tissue containing many fine vascular channels, abundant polymorphonuclear leukocytes, scattered eosinophiles, and fibroblastic proliferation. In the muscularis and serosa, both of which are slightly thickened, the same peculiar edematous areolar-like tissue loosely infiltrated by inflammatory cells is present. This lesion may be the result of chronic severe portal stasis with recently superimposed infection.

In the *myocardium* an occasional small scar is noted. Myocardial arteries are slightly thickened. The *lung* shows moderate passive hyperemia with some intra-alveolar edema and scattered acute inflammatory exudate in the small bronchi. Both the sections and blocks of *kidney* are missing. This is unfortunate in view of the clinical history and gross lesion at necropsy. The *prostate gland* shows in a few areas definite glandular hyperplasia. This, together with scattered corpora amylacea, produces an appearance usually associated with more advanced years than the actual age of the patient. The *adrenal glands* show moderate severe hyperemia in both the cortex and the medulla with small recent hemorrhages in a few areas of the cortex. In the *testicle*, spermatogenesis appears diminished, most of the tubules being lined by a single layer of cells. Interstitial cells are present in an abundant stroma. Sections of all four *parathyroid glands* are similar, with fairly normal pattern except for a slight increase of fat relative to the patient's age, and some vacuolization of the cytoplasm of the chief cells. The bony trabeculae and marrow of a sectioned *rib* are normal.

Summary of the Two Cases: Both patients presented a clinical picture of portal hypertension in which a prominent feature was evidence of marked collateral circulation about the umbilicus, including venous hum and thrill. In the second patient necropsy revealed a widely patent umbilical vein associated with an unusual type of fibrosis of the liver. This has strengthened the belief that we are dealing with examples of so-called "Cruveilhier-Baumgarten cirrhosis." Before developing this problem further, we are presenting a résumé of the data obtained by tabulating the cases reported in the literature (table 1).

Résumé of All Cases (Including the Authors' Two):

Age—The patients varied in age from 15 to 70 years with the following distribution:

Age in Years:	0–10	10–19	20–29	30–39	40–49	50–59	60–69	70–79	Not Stated
No. of Cases:	1	5	7	7	13	9	1	1	11

Sex—The patients' race was noted in only 10 instances; all of them were Caucasian.

Possible Etiologic Factors Mentioned. In the cases of Cruveilhier,[2] Baumgarten,[3] Bratiano [12] et al., and perhaps in our second case, hypoplasia of the portal system associated with congenital patency of the umbilical vein is considered to be the underlying cause of the clinicopathologic syndrome. In some of the other cases other etiologic factors were considered as of possible importance by the various authors: malaria in nine instances, alcohol in eight,

syphilis in six and trauma in one; the first three by inducing the hepatic changes, and the last by affecting the patency of the umbilical vein.

Symptomatology: The following symptoms were described most frequently: Abdominal swelling in 13 instances; epigastric pain and/or digestive disturbance, 12; hematemesis, 10; jaundice, 10; weakness, 8; prominent abdominal veins, 6; loss of weight, 4. No symptoms were recorded in 27 patients.

Physical findings: Most prominently mentioned were abdominal venous murmurs which were described in 44 of the cases with the following distribution of location; Epigastric in 26, umbilical in 14, epigastric and umbilical in 9, and elsewhere in the abdomen in 8. Palpably enlarged spleen was described in 31 cases; palpable thrill in 24; distended superficial thoracoabdominal veins in 23; palpable liver in 20; ascites in 15; peripheral edema in 7; and caput medusae in 3 cases.

Laboratory findings: Secondary anemia was present in 13 patients, leukopenia in 10, and a positive Wassermann test in nine.

Clinical diagnosis: The antemortem diagnoses in the group of 55 cases were as follows: Cirrhosis in 18 instances; Cruveilhier-Baumgarten disease, 13; Banti's disease, 4; undetermined, 18; nephritis, 1; congenital syphilis, 1.

Nineteen of the 54 patients were alive at the time of report in the literature. Of the remainder, 32 had come to autopsy. The following were then given as the immediate causes of death: Gastric hemorrhage, 5; hepatic insufficiency, 2; pneumonia, 1; pneumococcal sepsis, 1; pulmonary edema, 1; peritonitis, 1; bronchitis, 1; postoperative, 1; and not stated, 19.

Summary of Pathological Data: The liver was normal in size in two instances; small in 20, and enlarged in one. In 15 cases the surface was nodular, in three it was smooth. In 15 cases the liver was described as grossly cirrhotic. General atrophy was noted in three cases, atrophy of the left lobe alone was described in four, of the right lobe alone in four. Hypertrophy of the left lobe was mentioned in one, chronic passive hyperemia in one. The liver was not described in eight cases. Microscopically, cirrhosis was noted four times, " fibrosis " three times, and atrophy three times. No microscopic description was given in 25 instances.

The portal vein was recorded as grossly normal in six instances, abnormal in two, and not described in 21. Thrombosis of the portal vein was described twice, hypoplasia of the right branch twice, and thrombosis or stenosis of the hepatic veins in three cases.

The umbilical vein itself was recorded as patent in 14 instances; partially patent, 2; obliterated, 1; not described, 24. A large patent paraumbilical vein was described in 9 cases.

The spleen was grossly enlarged in 18 cases; normal, 1; small in none; showed chronic passive hyperemia in 1, and not described in 9 cases. Microscopically, it was noted that the spleen was normal in one instance; cellular with pulp increased in one; showed fibroadeny in one; thickening of trabeculae, 1; fibrosis, 4; chronic passive hyperemia, 1; and shrunken pulp, 1.

Discussion

It is evident from table 1 that there have been reported in the literature at least 52 cases, either under the title of Cruveilhier-Baumgarten disease, cirrhosis, etc.; or considered to belong in that group by authors reviewing the literature. The résumé of the tabulated data indicates that there is no specific disease process of similar etiology, clinical picture, and morbid anatomy, which will encompass all the reported cases. There is instead, a clinical syndrome based, when morphologic evidence was available, on a variety of morbid states. It is, however, possible that Cruveilhier and Baumgarten did describe a unique disease of specific etiology, clinical picture and morbid anatomy, and that later reports of similar but basically different disturbances have confused that issue. This would be analogous to the situation existing in the problem of Banti's disease. To discuss this question critically we wish to review briefly the original concept and criteria of Cruveilhier and Baumgarten. To understand their concept better it will be necessary to review the rôle of the umbilical vein in portal circulation. We shall then attempt to classify the reported cases according to these facts and summarize the important clinical features.

Cruveilhier considered the fundamental lesion to be a congenital patency of the umbilical vein. This patency he believed was probably due to maintenance after birth of an abnormal communication with the epigastric veins. This would prevent obliteration of the large umbilical vein. He then supposed that this would shunt blood away from the liver, and lead to atrophy of the liver. There is, of course, no evidence that a patent umbilical vein would shunt blood away from the liver unless the shunt led through the ductus venosus.

Baumgarten accepted most of Cruveilhier's concept as reasonable. He suggested that, in addition to the congenitally patent umbilical vein, congenital hypoplasia of the liver and portal system was present. Hypoplasia of the portal system would be a condition theoretically heightening portal venous pressure which would then shunt blood through a large patent umbilical vein to the systemic veins. There is some evidence that such a situation might produce further changes in the liver. Bainbridge and Leathes [13] found that experimental ligation of the portal veins in cats and dogs led to atrophy associated with marked periportal fibrosis. Fiessinger and Garling-Palmer [14] have found similar changes in only one out of eight dogs with experimental Eck fistulae. However, Rous and Larrimore [15] reported that experimental portal vein occlusion in rabbits led to atrophy in the involved areas without degenerative changes or connective tissue replacement.

There was thus developed by the original authors a concept which includes a definite etiology and morbid anatomy. The clinical picture is dominated by evidence of excessive umbilical circulation, including murmur and thrill, plus the implied evolution of portal hypertension leading to death. Final diagnosis would depend on necropsy, which should reveal patency of the um-

bilical vein itself (with communication with the epigastric veins) and an atrophic liver, the result of hypoplasia of the portal system. It is inferred from Baumgarten's descriptions that a certain amount of fibrosis might be present, secondary to the atrophic state of the liver; but typical or advanced cirrhosis is not considered part of the picture.

As one attempts to examine critically the data concerning the cases reported in the literature it becomes apparent that many cases have been included on insufficient evidence. Others do not at all correspond to the criteria or descriptions of the original authors. Much of the confusion has been introduced by cases in which umbilical circulation played a prominent rôle but in which the umbilical vein itself was not involved. In other cases, the umbilical vein itself was involved but only secondary to some independent preëxisting disorder. Before attempting a rational classification of the reported cases we wish to review briefly the rôle of the umbilical vein in portal circulation.

The development of the umbilical veins is closely related to the development of the portal system. In the early embryo the umbilical and vitelline veins are paired vessels and empty into the sinus venosus. As the liver parenchyma begins to form in the tissue of the septum transversum, there is interposed between these veins and the sinus venosum (later to form the atrium of the heart) a series of sinusoidal veins within the liver. These veins are formed by branching of the left umbilical and vitelline veins. The left umbilical vein also maintains a direct connection with the sinus venosum by means of the ductus venosum. The right umbilical vein disappears early. As the capillaries of the liver develop into their final state, the adult portal vein is developed from the vitelline veins and the left umbilical vein empties into the left branch of the portal vein and contributes to the sinusoids in the left lobe of the liver. Before birth most of the placental blood is shunted directly from the left umbilical vein to the atrium of the heart through the ductus venosum. The important rôle of the umbilical vein in the development of the portal system is well shown in figure 9 from Mall.[16] Baumgarten suggested that a congenital failure of the portal tree to develop would maintain umbilical vein patency and initiate the changes seen at autopsy, and be responsible for the clinical picture which the patients presented.

After birth and ligation of the umbilical cord, the umbilical vein atrophies to form the ligamentum teres within the falciform ligament, which process occurs within two months following birth, and the ductus venosum forms the ligamentum venosum. However, the upper portion of the umbilical vein remains patent into adult life as the Rest-Kanal of Baumgarten. Other vestigial veins which may occur will be described below. Normally there is no communication between the umbilical and the epigastric veins in the abdominal wall. The vestigial remnants of the retrogressive changes in the umbilical vein have no functional significance unless some disease process leading to portal hypertension invokes the development of all available collateral channels.

As McIndoe [17] has indicated, the collateral circulation following portal obstruction occurs in three general areas. The two most important areas are the anastomosis of portal tributaries with the terminations of the gastrointestinal tract, and the zones where the gastrointestinal tract or its appendages contact the retroperitoneal tissues or abdominal wall either through developmental relationship or pathological alteration. The third pathway of collateral circulation is through the obliterated embryologic circulation in the falciform ligament and is less frequently utilized. When this

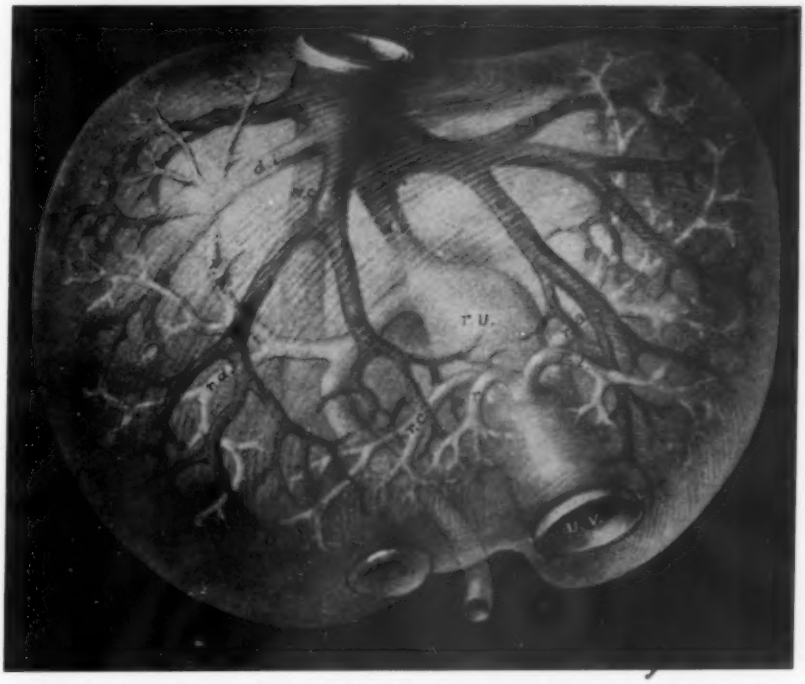

FIG. 9. Showing relationship of umbilical vein to development of portal system (after Mall, Franklin P., American Journal of Anatomy, 1905, v, 266; reproduced through the courtesy of the Wistar Institute of Anatomy and Biology, Philadelphia, Pa.; publishers).

pathway is utilized it is usually by anastomosis of the paraumbilical veins with the thoraco-abdominal veins. According to Weiss [18] this parietal system of veins is derived from six superficial veins, and five deep veins. Of the latter, the epigastric veins are important.

According to McIndoe,[17] the umbilical vein itself rarely participates in this collateral circulation, being " entirely obliterated a few days after birth." However, certain anatomic studies and dissections described in reported cases have established the existence of exceptions to this rule. We have previously alluded to the frequent patency of the terminal end of the umbilical vein in otherwise normal adults. This observation was made by Baumgarten [19] in 60 autopsies, and confirmed by Robin.[20] We have confirmed this occurrence

in several autopsies on children and adults with or without portal hypertension (figure 10). Plate 1 serves in part to illustrate the utilization of the Rest-Kanal in portal collateral circulation. In figure 1, the communication is

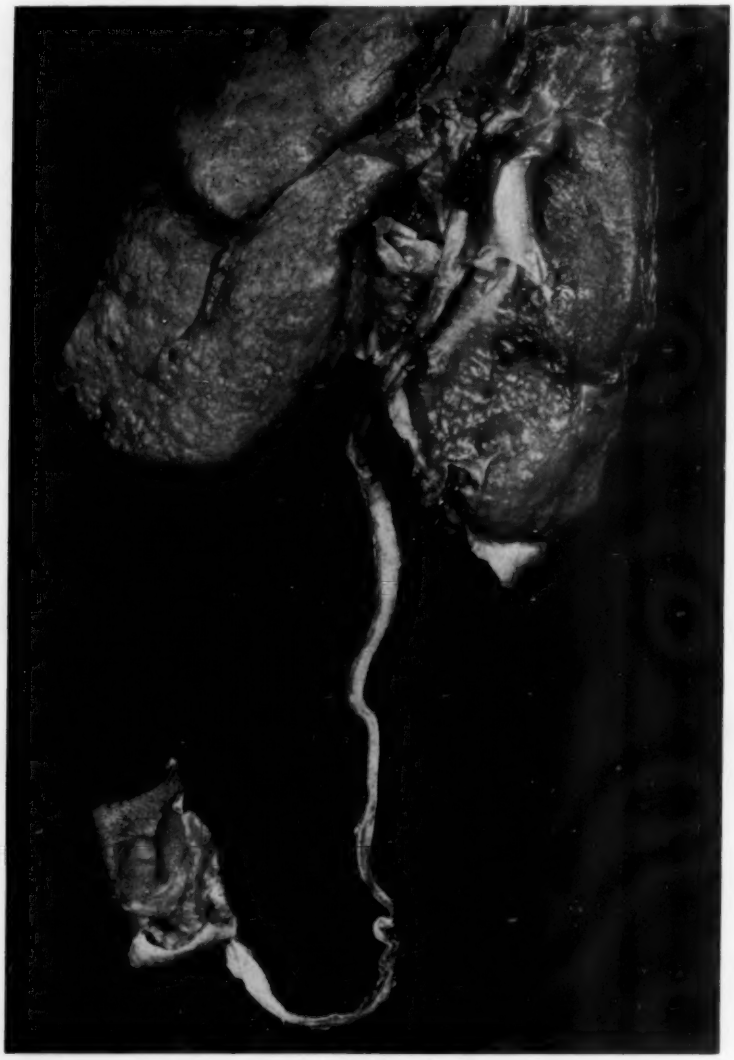

FIG. 10. Male, aged 12, dying of toxic cirrhosis with portal decompensation. A small Rest-Kanal was patent on injection. The remainder of ligamentum teres obliterated despite the presence of portal hypertension early in life.

by means of the vein of Burow (intercalary vein of Baumgarten) which runs properitoneally along the abdominal wall. In figure 2 one or more of the paraumbilical veins of Sappey may be unusually large and connect the Rest-Kanal with the epigastric veins.[21] These run in the ligamentum teres

and not subperitoneally, as does the vein of Burow. Not pertinent to the present discussion, but also shown in figure 2, are the more frequent connections of the paraumbilical veins of Sappey from the epigastric to the portal vein or its tributaries.[22, 23]

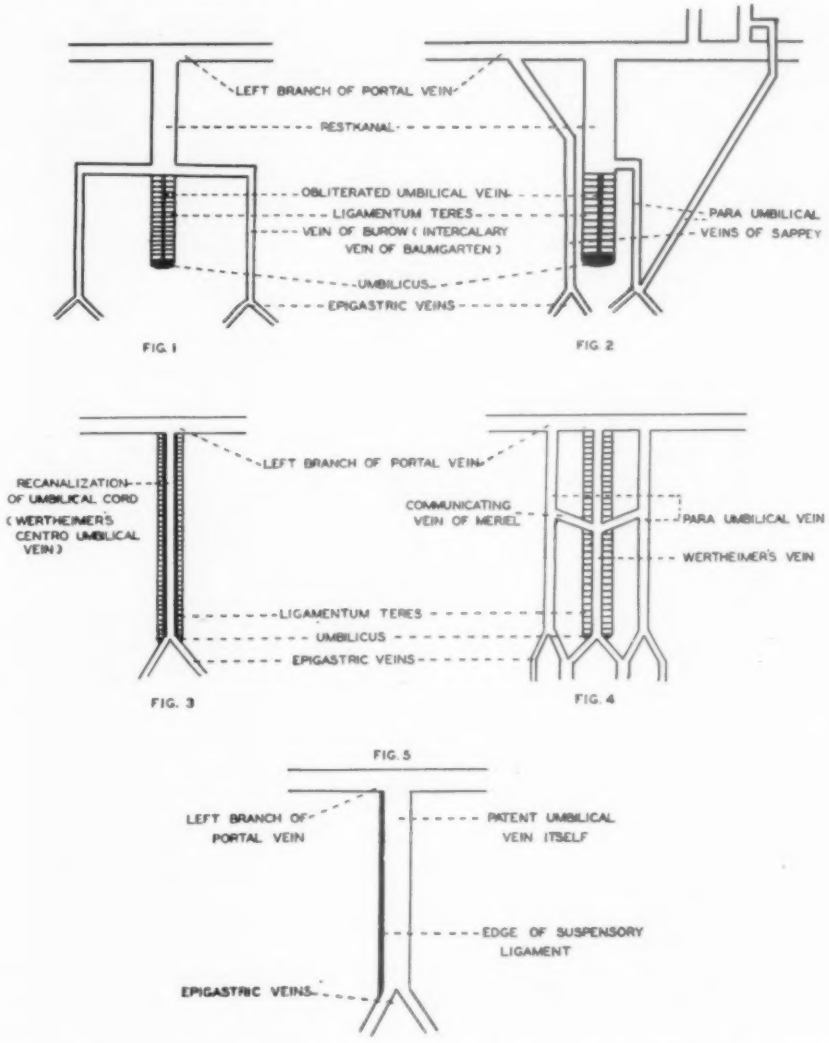

PLATE 1. Diagrammatic illustration of various reported means of utilization of umbilical vein in portal collateral circulation.

In figures 3 and 4 of plate 1 there is illustrated another means of utilization of potential communications of the umbilical vein in portal collateral circulation. Wertheimer [24] reported recanalization of the umbilical vein within the ligamentum teres to produce communication between the epigastric veins and left branch of the portal vein. This is illustrated in figure 3. In

figure 4, the situation is complicated by communicating veins as described by Meriel [25] between Wertheimer's vein and the paraumbilical veins.

Thus we see that in addition to the usual potential collateral connections of the paraumbilical veins with the thoraco-abdominal veins, there may occur

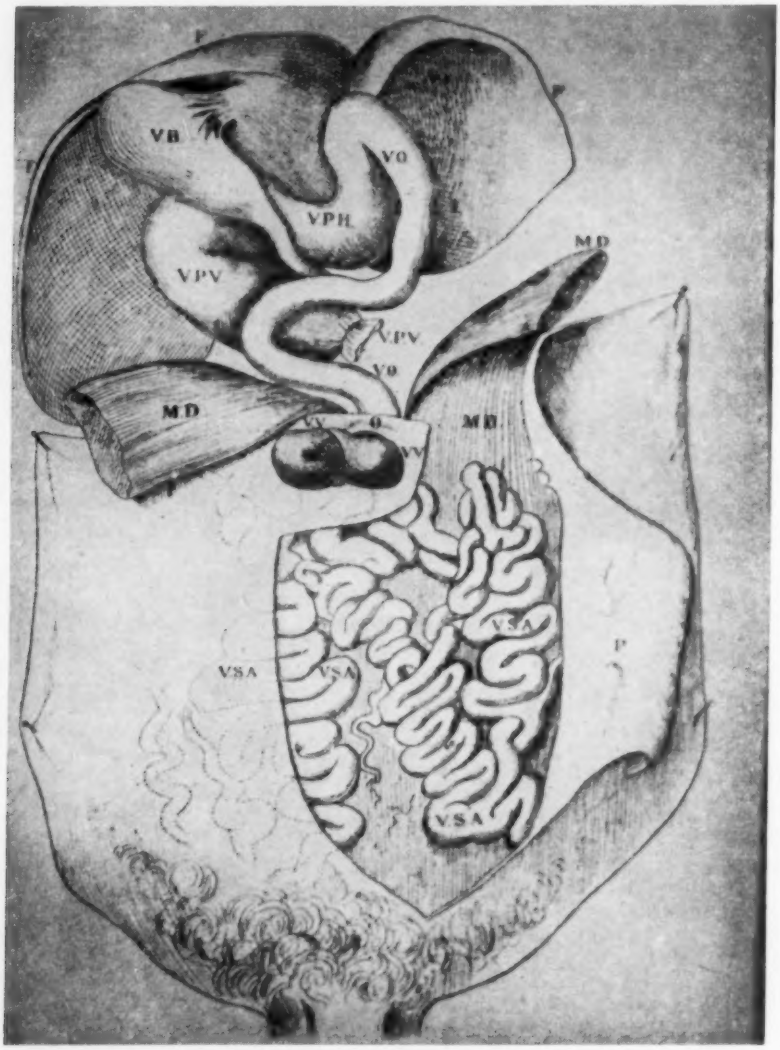

FIG. 11. Reproduction of illustration by Cruveilhier of original case reported by Pegot and Cruveilhier.

anastomoses of the latter veins through collateral channels furnished by the unobliterated portion of the umbilical vein itself. In either instance the excessive development of collateral circulation in this area in a patient with portal obstruction of whatever cause may lead to a clinical picture reported as an example of Cruveilhier-Baumgarten disease.

Finally, and most important in relation to this report, is the persistent patency of the umbilical vein itself. This is illustrated in figure 5 of plate 1. Here the vein is of the same size or larger than in fetal life and no ligamentum teres is present. It runs along the inferior margin of the suspensory ligament. Such a completely patent umbilical vein was first described as an incidental finding at autopsy by Manec [26] and Menière.[27] The association of this finding with atrophy of the liver, large spleen, and portal decompensation was first described by Pegot [1] and Cruveilhier.[2]

We have thus elaborated the part played by the umbilical vein in portal circulation, and have shown its potential collateral connections in portal hypertension, apart from the more usual connections through the paraumbilical veins. We have already alluded to the contention that a congenital patency of the umbilical vein either alone (Cruveilhier) or associated with congenital hypoplasia of the portal system (Baumgarten) may constitute an individual disease entity. It also became apparent that any other disease resulting in portal hypertension which happens to utilize umbilical collaterals excessively, will produce a very similar if not identical clinical picture. The difficulties of classification of such cases is thus evident. Even the autopsy may not permit complete classification, since some of the changes seen, e.g., fibrosis or cirrhosis in the liver, might be secondary to maldevelopment of the portal system. However, if one takes into consideration the original concept of Cruveilhier and Baumgarten, together with the points already brought out in the discussion, the reported cases in the literature (table 1) can be roughly divided into the following groups:

1. Patency of the umbilical vein itself
   A. Associated with the other clinical and pathological findings as described by Cruveilhier and Baumgarten; cases 1, 7, 19, 21, 25, and our second case (case 55 in table 1).

Here there is a clinical picture of portal hypertension with excessive umbilical circulation, and necropsy reveals patency of the umbilical vein itself, atrophy of the liver with little or no cirrhosis and splenomegaly. Any hepatic fibrosis which may be present is thought to be secondary to atrophy associated with portal hypoplasia. The etiology is presumably congenital patency of the umbilical vein associated with hypoplasia of the portal system. In cases 1 and 2, the authors also list other factors of possible etiological significance.

B. Associated with some independent disease of the liver or portal system resulting in portal hypertension, viz.:

1. Advanced portal cirrhosis, cases 24, 27, 42, 44, 46, 53.
2. Anomaly or occlusion of the hepatic veins, cases 32 and 47.

In this group of cases the assumption is that some disease of the liver or portal system had developed in a patient who happened coincidentally to have available a congenitally patent umbilical vein. The latter then dominated

the collateral circulation and led to the clinical picture as seen in Group A. Case 53 is an interesting example of how portal hypertension at birth (the result of toxic hepatitis and cirrhosis) may have served to keep the umbilical vein patent. The cases of primary hepatic vein disease, despite the contentions of some of the reporting authors, are obviously quite different in origin from the original cases of Cruveilhier and Baumgarten. The coincidental existence of a patent umbilical vein has led to their being reported in this group. Some of the cases in Group I B where advanced portal cirrhosis is present, may perhaps be true cases of Cruveilhier-Baumgarten disease where the hepatic lesion has progressed to a severe grade of cirrhosis.

II. Cases where there is some disease of the liver or portal system resulting in portal hypertension in which collateral circulation through the umbilical area *apart from the umbilical vein* plays a prominent rôle.

A. Cases of portal cirrhosis of the liver associated with unusually prominent paraumbilical veins, cases 2, 4, 6, 12, 26, 34, 50.

This is the largest subgroup and is the probable situation in most cases of cirrhosis with loud venous hum, murmur, or marked caput medusae.

B. Excessively prominent paraumbilical veins with portal hypertension other than cirrhosis of the liver.

Case 40, hypoplasia right branch of the portal vein, atrophy of liver, no cirrhosis, and patency of paraumbilical vein.

C. Patency of other collaterals in the umbilical area, in association with cirrhosis or other causes of portal hypertension.

This refers largely to the utilization of collateral channels in the umbilical area furnished by remnants of the umbilical vein, as indicated in plate 1. The most frequent cause of the portal hypertension in these cases is cirrhosis of the liver.

Examples: 1. Case 16, cirrhosis of liver plus patent vein of Burow.
2. Case 22, cirrhosis of liver plus patent Wertheimer's vein.
3. Case 33, stenosis of hepatic vein orifices, together with patency of Wertheimer's (central) vein.

III. Cases with a clinical picture considered as Cruveilhier-Baumgarten disease, cirrhosis, etc., but without adequate necropsy confirmation. This is the largest group, comprising 30 cases, which can be divided into three subgroups, as follows:

A. Cases with the clinical picture of Cruveilhier-Baumgarten disease who were alive at time of report, cases 5, 8, 9, 13, 17, 18, 28, 29, 31, 35, 37, 38, 39, 43, 49, 51, 52, and our first case (53 in table 1).

B. Cases with clinical picture of Cruveilhier-Baumgarten syndrome who had died but had not been necropsied, cases 15, 20, 36, 41, 45.

C. Cases with clinical picture of Cruveilhier-Baumgarten syndrome which came to necropsy, but had inadequate description of the umbilical circulation, cases 3, 10, 11, 16, 23, 30, 48.

Proper autopsy study in Group III would have led in most cases to classification in one of the other groups.

We have thus outlined a classification of all cases that have been considered as having the clinical picture of Cruveilhier-Baumgarten syndrome, i.e., symptoms and signs of portal hypertension with evidence of excessive umbilical circulation in the form of a loud murmur or thrill. It is evident that the clinical picture dependent on portal hypertension associated with intense umbilical collateral circulation can be produced by a variety of etiologic factors combined with a variety of anatomical arrangements of the umbilical circulation. It is therefore impossible to limit the clinical diagnosis to any given group of pathological findings. To attempt to do so would introduce the same confusion as has resulted from attempting to delineate rigidly a case of Banti's disease according to Banti's clinicopathological criteria, the clinical aspects of which overlap with so many other conditions. It should therefore be recognized that any patient having portal hypertension, generally with splenomegaly, and in whom evidence in the form of visible veins, murmur and thrill of excessively prominent umbilical circulation exists, merits the diagnosis of *Cruveilhier-Baumgarten syndrome.* Further etiologic and pathogenic evaluation of the case will be dependent on the necropsy findings, especially in the liver, portal system, umbilical circulation. *Those cases which show at necropsy patency of the umbilical vein itself together with atrophy and little or no fibrosis of the liver would then be considered as examples of Cruveilhier-Baumgarten disease.* The term "Cruveilhier-Baumgarten cirrhosis" is undesirable since no particular type of cirrhosis has been proved to exist, and since, in fact, Cruveilhier and Baumgarten denied the importance of cirrhosis in the disease process.

Why then should the terminology "Cruveilhier-Baumgarten syndrome" be preserved? Why not consider these cases simply as examples of portal obstruction in which the umbilical collateral route has been used more abundantly than usual, such as the ordinary concept of caput medusae implies? We believe this designation should be preserved because

1. The clinical picture that includes intense umbilical circulation is rarely due to the use of ordinarily available collateral channels in the umbilical area. More likely, these findings signalize the existence of some unusual umbilical collateral as previously discussed, perhaps patency of the umbilical vein itself.

2. The small group of cases where the umbilical vein itself is patent constitutes a separate congenital anomaly. When this anomaly is combined with simple atrophy or minimal atypical cirrhosis, the theoretical proposals of Cruveilhier and Baumgarten of a separate entity to explain these cases must then be a consideration. Until such contentions are established or dis-

proved it should be worth while to segregate similar future cases in the literature under this title.

3. Since it is impossible to distinguish the above group of cases from other disorders simulating them without careful autopsy examination (as indicated by cases reported in the literature) it becomes useful to designate the entire group as "Cruveilhier-Baumgarten syndrome."

Having thus outlined our concept of the nature of the Cruveilhier-Baumgarten disease, and shown the unfortunate need of incorporating these cases within a clinically indistinguishable group entitled Cruveilhier-Baumgarten syndrome we should like to recapitulate the essentials of the clinical picture of the Cruveilhier-Baumgarten syndrome. It may be possible to point out some minor differences helpful in distinguishing the smaller group of cases of Cruveilhier-Baumgarten disease.

The analysis of the reported cases indicates that the most frequent presenting symptoms, such as abdominal distention, digestive disturbances and hematemesis, are manifestations of portal hypertension. In general, the symptoms of the original disease causing the portal hypertension are usually absent or obscure. In the group of Cruveilhier-Baumgarten disease the age of onset of symptoms was less than in the whole group so that three of the five cases died before the age of twenty-five.

The principal physical findings, as indicated in the résumé of reported cases, are abdominal venous murmur and thrill, splenomegaly and dilated thoraco-abdominal veins. Caput medusae was mentioned by name in only four instances. Palpable liver was also a frequent finding during life (none enlarged at autopsy). Most of these signs are again related to the portal hypertension. The murmur and thrill are of most interest and diagnostic importance, since they depend directly on the venous anastomoses. They are usually loudest at the umbilical or epigastric regions, and generally continuous. The production of the murmur probably depends on the passage of blood to an area of different caliber or direction, or the eddying of current in a blind, dilated venous sac or pouch. The murmur might also be produced at points of constriction in the course of a dilated and tortuous vein. There is no apparent difference in the character of the murmur or thrill within the group of Cruveilhier-Baumgarten disease, although one might expect them to be most pronounced because of the larger size of the patent umbilical vein.

Splenomegaly is another fairly constant physical sign. Portal hypertension is common to all cases of the syndrome and contributes its share to the enlargement of the spleen in the form of chronic congestive splenomegaly. Other factors such as direct injury and irritative hyperplasia of the splenic reticulum may also be a factor in some of the cases. It is interesting to note that all five cases of Cruveilhier-Baumgarten disease have definite and frequently marked splenomegaly. The findings and problem with regard to the splenomegaly are similar to that of so-called Banti's dis-

ease. Baumgarten's explanation of the spleen "taking over the function of the liver" is of course antiquated. He did, however, invoke portal hypertension as part of his explanation for the splenomegaly.

The leukopenia and secondary anemia reported in many of the cases are again probably related to the portal hypertension and splenomegaly. Positive blood Wassermann tests as evidence of syphilis occurred in approximately 15 per cent of the reported cases.

The clinical diagnosis most frequently made in the entire group was some form of cirrhosis of the liver. In 13 of the reported cases Cruveilhier-Baumgarten disease was suspected before death. In many instances the case was reported as such even when the autopsy findings did not conform to the original descriptions and criteria. The decision to consider a case clinically or pathologically as an example of Cruveilhier-Baumgarten disease may, in our opinion, frequently have been made because the physician or pathologist was impressed with the evidence of excessive umbilical circulation, without giving due critical attention to other necessary criteria.

Prognosis and Treatment

Most of the reported cases have died of portal decompensation or hepatic insufficiency. The duration of life after the clinical picture is established varies somewhat with the underlying cause of the syndrome. Some of the authors have contended that the widely patent umbilical vein would tend to delay the development of portal decompensation and diminish the frequency of gastric hemorrhage. However, in the group of Cruveilhier-Baumgarten syndrome, where the umbilical vein itself was patent the average age at death was 30.4 years as compared to 38.2 for the entire unselected group.

Since the clinical picture is usually dominated by progressive and usually fatal portal decompensation, the treatment consists largely of attempts to symptomatically alleviate this condition. Splenectomy is thought to be of no value and particularly contraindicated because of the danger of hemorrhage from the greatly dilated venous channels in the abdominal wall. Similarly, in doing paracentesis or peritoneoscopy great caution must be observed to avoid the large veins. Peritoneoscopy may be of value in demonstrating a large umbilical vein and in permitting biopsy of the liver in suspected cases of Cruveilhier-Baumgarten syndrome.

Summary and Conclusions

Our interest in the subject of Cruveilhier-Baumgarten disease was aroused by the two cases which we have presented. The data which we have been able to obtain from the original case reports of Cruveilhier and Baumgarten and of all subsequent reports have herein been reviewed. We believe that the term "Cruveilhier-Baumgarten syndrome" may be applied to patients having a clinical picture of portal hypertension featured by a loud

abdominal murmur and thrill. The less important further details of this syndrome have also been enumerated. Those cases that prove at necropsy to have the pathologic criteria as originally outlined should then be considered as examples of Cruveilhier-Baumgarten disease. We believe our second case fulfills these criteria and becomes the fifth case of Cruveilhier-Baumgarten *disease* on record, and that our two cases increase the total number of reported cases of Cruveilhier-Baumgarten *syndrome* to date to 55. We believe the preservation of this name as applied to the syndrome is indicated because of the fairly uniform clinical picture centered about the loud murmur and thrill. More important is the advisability of maintaining the integrity of a distinct disease of separate etiology and pathologic features, as delineated in the picture of Cruveilhier-Baumgarten *disease*. We have therefore taken the liberty of reviewing the subject and of introducing in the English literature a new terminology for certain cases of portal system disease at the risk of creating similar confusion to that existing with regard to Banti's disease. We believe, however, that an understanding of the original criteria will avoid such confusion and thus allow us to add to our diagnostic evaluation and understanding of certain patients presenting the clinical picture of portal hypertension.

REFERENCES

1. Pegot: Anomalie veineuse, Bull. Soc. anat. de Paris, 1833 in-8, t. vii, pp. 108–109. Tumeur variqueuse avec anomalie du système veineux et persistance de la veine ombilicale, développement des veines souscutanées abdominales, Bull. Soc. anat. de Paris, 1833, xlix, 57.
2. Cruveilhier, J.: Traité d'anatomie pathologique générale, 1852, Chez J. B. Baillière, Paris. (Vol. II, viii classe, 3 ordre, p. 315.) Anatomie pathologique du corps humain, 1829–1835, Chez J. B. Baillière, Paris. (Vol. I, xvi^{e} livr., pl. vi—Maladies des veines.)
3. Von Baumgarten, P.: Ueber Vollstängiges Offenbleiben der Vena umbilicalis; zugleich ein Beitrag zur Frage des Morbus Bantii. Baumgarten Arbeiten, 1908, 6. (Arb. a. d. geb. d. path. Anat. . . . Inst. zu Tübing., Leipzig, 1907, vi, 93–110.
4. Hanganutz, Marius: Sur la cirrhose de Cruveilhier-Baumgarten, Presse méd., 1922, lxviii, 20.
5. Galibern, André: Cirrhose de Cruveilhier-Baumgarten. Thèse: Université de Montpelier Faculté de Médecine, No. 46, June 1935.
6. Thayer, W. S.: Of the presence of a venous hum in the epigastrium in cirrhosis of liver, Am. Jr. Med. Sci., 1911, cxli, 313–327.
7. Henry, J. N.: Report of a case of loud venous hum heard over the xiphoid cartilage in cirrhosis of the liver, Am. Jr. Med. Sci., 1912, cxliii, 72.
8. Wollaeger, E. E., and Keith, N. M.: Epigastric thrill and murmurs in a case of cirrhosis of the liver with general vascular signs of arteriovenous fistula, Proc. Staff Meet. Mayo Clin., 1938, xiii, 33.
9. Moschkowitz, Eli: Critique of Banti's disease, Jr. Am. Med. Assoc., 1917, lxix, 1045–1051.
10. Johnson, John M.: Relation of changes in the portal circulation to splenomegaly of the Banti's type, Ann. Int. Med., 1931, iv, 772–782.
11. Meyer, A. W.: Retrogressive changes in the fetal vessels and the suspensory ligament of the liver, Am. Jr. Anat., 1914, xvi, 477.

12. Bratiano, S., Visineano, N., and Salomon, E.: Le syndrome (cirrhose) de Cruveilhier-Baumgarten, Ann. d'anat. path., 1929, vi, 293.
13. Bainbridge, F. A., and Leathes, J. B.: The effect of arterial or venous obstruction upon the nutrition of the liver cells, Biochem. Jr., 1907, ii, 25–33.
14. Fiessinger, Noel, and Palmer, Raoul G.: L'Altération eloignée du parenchyme hépatique chez les chiens porteurs de fistules d'Eck, Rev. méd. de la Suisse Rom., 1935, lv, 76–80.
15. Rous, P., and Larrimore, L. D.: The relation of portal blood to portal maintenance, Proc. Soc. Exper. Biol. and Med., 1919–1920, xvii, 65.
16. Mall, Franklin P.: A study of the structural unit of the liver, Am. Jr. Anat., 1905–1906, v, 227.
17. McIndoe, Archibald H.: Vascular lesions of portal cirrhosis, Arch. Path., 1928, v, 23.
18. Weiss, Samuel: Diseases of the liver, gallbladder ducts and pancreas, Paul B. Hoeber & Co., Inc., New York, 1935, p. 387.
19. von Baumgarten, Paul: Ueber das Offenblieben foetaler Gefässe, Centralbl. f. Med., 1877, xv, 721.
20. Robin, C.: Sur un point d'anatomie pathologique relatif à l'histoire de la cirrhose, par Sappey, Bull. de l'Académie Impériale de Médecine, 1858–1859, xxiv, 943–995.
21. von Baumgarten, Paul: Ueber die Nabelvene des Menschen und ihre Bedeutung für die Circulationsstörung bei Lebercirrhose, Arb. a. d. Geb. d. path. Anat. Inst. zu Tübingen, Leipzig, 1891, i, 1–46.
22. von Baumgarten, Paul: Ueber das Nabelvene des Menschen, Arbeiten von Tübingen, 1891.
23. Eppinger, H., and Ranzi, E.: Die Hepato-lienalen Erkrankungen. Second Case, Julius Springer, Berlin, 1920, p. 407.
24. Wertheimer, R.: Récherches sur la veine ombilicale, Jr. de l'anat. et physiol., 1886, xxii, 1–15.
25. Meriel, E.: Note sur le système veineux para-ombilico-vésical, Bull. et mém. Soc. anat. de Paris, 1902, 6S, iv, 469–471.
26. Manec, L.: Récherches anatomico-pathologiques sur la hernie crurale, Paris, 1826, in–4.
27. Menière, M.: Observations relatives à une anastomose remarquable du système veineux général avec le système veineux abdominal, Arch. de Med., Paris, 1826, 4me Année, x, 381–388.

ADDITIONAL BIBLIOGRAPHY

These are mostly tabulated and reported cases to which reference was not made in the text.

Audry, J.: Note sur les souffles veineux continues de la région sus-ombilical, Lyon méd., 1932, lxx, 359–391.

Bamberger, H.: Granulirte Leber. (Abstract.) Carl Christian Schmidt's Jahrbücher der in- und ausländischen gesamten Medicin, Leipzig, 1851, lxxii, 195–197. (Original article in Wien. med. Wchnschr., 1851, No. 1, p. 6.)

Bastai, R.: Aplasia delle vene suprahepatiche con persistenza delli vene ombilicale, Policlinico (sez. med.), 1925, i, 1.

Benque, W.: Ein Fall von Persistenz der Vena umbilicalis mit anderen Anomalien, unter dem Bilde des Morbus Banti, Wien. klin. Wchnschr., 1912, xxv, 1249.

Bordoni, L.: Di una anastomosi fra la vene epigastrica e l'ombilicale nel feto umano, Atti della Soc. di Science Naturali di Pisa, 1885.

Bordoni, L.: Nota clinica su di un caso di cirrosi epatica malarica (considerazioni sul soffio venoso epigastrico). Atti Cong. gen. d. Ass. med. ital. 1891, Siena, 1893, xiv, 151–154. Also—Sperimentale, Firenze, 1891, lxviii, 433–437.

Bouvillaud—Le Maire: Quoted by Galibern.[5]

CATTI, GEORG: Ueber Venengeräusche bei der interstitiellen Hepatitis, Ztschr. f. klin. Med., Berlin, 1907, lxi, 269–280.

CHABROL, E., and BERNARD, H.: Splénomégalie par pyléthrombose, phlébite iliaque secondaire, Bull. et mém. Soc. méd. d. hôp. de Paris, 1928, lii, 9–12.

DAVIES, H.: (1863) Quoted by GALIBERN.[5]

FIESSINGER, NOEL, and BRODIN, PAUL: Le syndrome ictéro-ascitique des hépatites scléreuses, Presse méd., 1924, xii, 121–123.

FIESSINGER, N., and MICHAUX, L.: A propos de la cirrhose de Cruveilhier-Baumgarten. Deux cas nouveaux, Bull. et mém. Soc. méd. d. hôp. de Paris, 1930, xlvi, 88.

FIGUERIDO, ALVARO, and DE GONDRA, J. M.: Cirrosis de Cruveilhier-Baumgarten, Arch. de Ap. Digestivo, Mayo, 1930. Cirrosis de Cruveilhier Baumgarten, Arch. de med., cir. y espec., 1930, xxxii, 197–201.

FLORAND, ANTOINE: Souffles continus xyphoiden et sous-ombilical d'origine veineuse chez un cirrhotique (1), Bull. et mém. Soc. méd. d. hôp. de Paris, 1922, xlvi, 3d S., 1342–1346. Souffle continu au niveau de l'appendice xyphoïde, Bull. et mém. Soc. méd. d. hôp. de Paris, 1917, xli, 866.

FONTANEL, P., and PUIG, R.: Le souffle veineux paraxyphoidien et la cirrhose de Cruveilhier-Baumgarten, Jr. de méd. de Lyon, 1931, xii, 89.

FORNS, J. S., and BARCELO, P.: Consideraciones Sobre la cirrosis de Cruveilhier-Baumgarten, Rev. de Barcelona, 1935, xxiii, 411.

GIACCOMINI, C.: Sopra di un umpra communicazione tra la vena porta a la vene iliache destre, Giov. d. accad. di Med. di Tovino, 1873, 3. S., xiv, 587–621.

GALLAVARDIN, GRAVIER, and PUIG, R.: Bruit musical continu chez un cirrhotique. Bruit derouet cave, Soc. med. d. hôp. de Lyon, 1928 (March 20).

GAMBARATI, V.: Sopra un caso di soffio venosa udibile sull ala area epatica in individuo affecta da cirrosi epatica volgare, Reforma med., Roma, 1903, xix, 153–156.

GINGOLD, NADOR: Consideratiuni aspra sindromului Cruveilhier-Baumgarten. Teza pentru Doctorat. Bucuresti, 1929 (December 17).

GUEZ, J.: A probable case of Cruveilhier-Baumgarten cirrhosis, Tunisie Méd., 1936, xxx, 138.

VON JAKSCH: Ueber ein intra-abdominales Venensgeräusch in Verlaufe der chronischen interstitiellen Leberentzündung, Prager med. Wchnschr., 1895, xx, 13–14.

KAUFMAN, E.: Un cas de cirrhose de Cruveilhier-Baumgarten, Monde médical, N. 755, 1929 (September 1).

LUPU, N. G., and GINGOL, N.: Un cas de syndrome de Cruveilhier-Baumgarten. Quelques considérations sur la pathogénie de ce syndrome, Bull. et mém. Soc. méd. d. hôp. de Bucarest, 1929, I, 271–278.

LUTEMBACHER, R.: Bruits de souffle veineux et cirrhose de Laennec (cirrhose de Cruveilhier-Baumgarten), Presse méd., Paris, 1936, xliv, 847.

MASUDA, NIRO: Ueber einen Fall Morbus Banti bei vollständingem Offenbleiben der Vena umbilicalis, Med. Klin., 1911, vii, 104–106.

MOUKTAR, AKIL: Souffle continu, xyphoïdien au cours d'une pyléphlébite, Soc. méd. d. hôp. de Paris, 1924, 3d Series, xlviii, 572–575.

OETINGER, W., and MARIE, R-L.: De la maladie de Banti, Rev. de méd., 1911, xxxi, 345–363.

PAGNIEZET and RIVOIRE: Un cas de cirrhose de Cruveilhier-Baumgarten, Soc. méd. d. hôp. de Paris, 1929 (December 20).

PIAZZA-MARTINI, V.: Del rumore di soffio venoso udibile sull'area epatica, Riforma med., Napoli, 1894, x, 663, 673, 687.

PICCHINI, L.: Contributo allo studio del soffio e fremito epigastrico nella cirrosi epatica. Segno Firenzo. 1890–1891, i, 326–364: il Segno, fasc. 12.

POPPER, M.: Sur un cas de syndrome de Cruveilhier-Baumgarten, Bull. et mém. soc. méd. d. hôp. de Bucarest, 1923–1924, v–vi, 244–248.

RAOUL-DUVAL, PH.: La cirrhose de Cruveilhier-Baumgarten. Etude anatomique, clinique et classification symptomatique, Thèse Paris, 1931.

ROLLESTON, H. D.: Diseases of the liver, etc. 1905, W. B. Saunders, Philadelphia, p. 238.

SAPPEY, C.: Recherches sur quelques veines portes accessoires, Compt.-rend. Soc. de biol., 1859, 3d Series, 1, pt. 2, 3–13.

SCHEELE, L.: Ueber einige seltenere Nonnengeräusche und ihren diagnostischen Wert, Internat. Beitr. z. inn. Med., Berlin, 1902, ii, 41–58.

SPINELLI, A., and PANA, C.: Occlusione delle vene sovraepatiche con obliterazione della vena cava inferiore e di tutte le sue collaterali, con persistenza della vena ombelicale (sindrome di Cruveilhier-Baumgarten) e ginecomastia, Riv. di clin. med., 1934, xxxv, 499–551.

TAYLOR, F.: Cases of cirrhosis of the liver in children with some remarks on cirrhosis, Guy's Hosp. Rep., 1895, lii, 45–75.

TROUSSEAU, A., and SAPPEY, C.: Quoted by GALIBERN.[5]

VISINEANO, N.: Contributiuni la studiul sindromului Cruveilhier-Baumgarten. Un caz prin anomalie portala si persistenta venei paraombilicale, Teza Bucuresti, 1928.

CASE REPORTS

ACUTE HEMOLYTIC ANEMIA, AUTOAGGLUTINATION, TOXIC HEPATITIS AND RENAL DAMAGE FOLLOWING SULFATHIAZOLE THERAPY; CASE REPORT *

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SOON after the introduction of sulfanilamide into this country reports of various toxic manifestations following its use began to appear, among them reports of acute hemolytic anemia. Acute hemolytic anemia due to sulfanilamide administration was first described by Harvey and Janeway [1] in 1937 and since then has been noted by many other observers. In a large series of cases the incidence of this complication following sulfanilamide has been estimated as approximately 2.5 per cent of all adults and 8.5 per cent of all children receiving the drug.[2] Later studies have revealed an incidence of 1.8 per cent in all patients.[3] Hepatitis as a toxic reaction to sulfanilamide was first described by Bannick, Brown and Foster in 1938.[4] In the following year, Antopol and his associates reported two cases of acute hemolytic anemia following sulfanilamide therapy in which autoagglutination of the blood was present.[5] We have not as yet encountered further reports of the latter complication of sulfonamide therapy. In 1940, Spring and Bernstein reported two cases from this hospital in which there was a coexistence of toxic hepatitis, acute hemolytic anemia and renal damage following sulfanilamide therapy.[6] They noted that up to that time there was only one doubtful case reported with this combination of complications. Acute hemolytic anemia following sulfapyridine administration has been reported,[7] and its incidence appears to be less than that of sulfanilamide.[8]

Sulfathiazole (2-para-aminobenzenesulfonamidothiazole), the thiazole analogue of sulfapyridine, was introduced by Fosbinder and Walter [8] in August of 1939, and by Lott and Bergeim shortly thereafter.[9] Experimental investigations by Van Dyke, McKee and others indicated that the new drug was of approximately the same order of toxicity as sulfapyridine.[10, 11] During the past year many investigators who have used sulfathiazole in the chemotherapy of bacterial infection have become convinced of its efficacy in staphylococcic, pneumococcic and gonorrheal infections, and as a result of these clinical trials the drug is now generally considered to have comparatively low toxicity. A review of the literature, which is too lengthy to be summarized in a paper of this type, reveals no cases of acute hemolytic anemia in man due to sulfathiazole as far as we could ascertain, although a few instances of moderate anemia have been men-

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tioned. The case to be reported is one of acute hemolytic anemia, autoagglutination, toxic hepatitis and renal damage following sulfathiazole therapy in a pneumococcus type VII lobar pneumonia with recovery.

Case Report

J. K., aged 45, white male, a tailor by occupation, was admitted to the medical service of Dr. Henry Schumer, The Bronx Hospital, on November 18, 1940, with a chief complaint of persistent chills and fever of three days' duration. He had felt entirely well until November 15, at which time he felt a draft and noted a stiffness of the neck. He also felt a pinching sensation in the left infrascapular region and about the left ear, lasting several minutes at a time. Toward evening there were chilly sensations, fever and anorexia. On the following day the patient had two series of severe chills, with a fever of 105° F. On the day before admission hoarseness developed, and there was one episode of vomiting. Chills and high fever continued, and hospitalization was advised.

The past history was negative except for an inflammation of the left eye due to a foreign body. The patient had been in this country for 20 years.

Physical examination revealed a fairly well-developed and nourished male who appeared acutely ill and dyspneic. The right eye was normal. The left eye was capable of perceiving only light and the pupil was fixed in mid-dilatation. The left fundus oculi showed evidence of secondary optic atrophy. The teeth were in poor condition, and the tongue dry. The lungs revealed dullness, increased fremitus, bronchophony and bronchial breath sounds over the left lower lobe with occasional medium moist râles. The blood pressure was 116 mm. Hg systolic and 74 mm. diastolic, and the pulse rate 140. The heart sounds were fair and no adventitious sounds were present. The abdomen and extremities were normal.

The admission diagnosis was lobar pneumonia of the left lower lobe and amblyopia of the left eye, probably on the basis of an old inflammation following implantation of a foreign body.

Clinical course. The patient's temperature on admission was 105° F., and chemotherapy was withheld because of a rapid drop of the temperature to 102.6° F., this being interpreted as a possible sign of spontaneous resolution. However, on the next day, the temperature again rose to 104° F. The patient became suspicious of all physicians and attendants and cried out that he was "going to die" and that "food was being forced on him to poison him." His condition was interpreted by the consulting psychiatrist as a borderline toxic psychosis of the paranoid type. Sulfathiazole therapy was begun that evening with an initial dose of 2 grams, followed by 1 gram doses every four hours for the next 48 hours, a total dose of 17 grams being administered. The temperature during this time fell by rapid lysis and was normal for 12 hours before the drug was discontinued.

The admission blood count showed a hemoglobin of 94 per cent Sahli (13.6 grams), and the erythrocytes numbered 4,900,000 per cu. mm. There was a leukocytosis of 16,000, with 56 per cent neutrophiles, 33 per cent band forms, six lymphocytes, four monocytes, and one Turck cell. The urine was negative. The sputum was sanguinous and mouse inoculation revealed pneumococcus type VII. Roentgen-ray of the chest at the bedside exhibited pneumonic consolidation of the left lower lobe. The blood chemistry was normal, and the blood culture was sterile at the end of 144 hours' incubation. The blood Wassermann and Kahn tests were both three plus positive.

Forty-eight hours following the onset of the psychosis, the sensorium was clear, and the patient was well-oriented and coöperative. The psychiatrist found him en-

tirely recovered mentally. The chest signs showed clearing, and the patient was thought to be recovering.

However, on November 24, the seventh hospital day, the temperature rose suddenly from normal to 103° F. On the following day the temperature varied between 101° F. and 102.2° F. and the chest signs, i.e., dullness, bronchial breathing and bronchophony extended anteriorly and higher posteriorly. This was thought to indicate an extension of the pneumonic process, and sulfathiazole therapy was resumed in the same dosage (one gram every four hours). Radiograph of the chest at this time showed clearing of the pulmonic process. Temperature and pulse continued to be elevated. The sputum was now negative for type-specific pneumococci and also tubercle bacilli. By the twelfth hospital day, November 29, the blood sulfathiazole concentration had risen to 8.0 mg. per cent.

Despite this high sulfathiazole level, severe chills and spiking fever up to 105.4° F. occurred during the next two days, November 30 and December 1. Type VII antipneumococcic rabbit serum was then given in two divided doses without reaction, the total dosage being 108,000 units. Blood culture done at this time was sterile. Following the serum therapy, the fever dropped to about 102° F. for the succeeding two days, December 2 and 3. The hemoglobin at this time had fallen slightly to 82 per cent and the leukocytes to 11,900 per cu. mm. On the afternoon of December 3, the temperature rose to 103.4° F. and the sulfathiazole was discontinued as this was thought possibly to be a drug fever. Following this, the temperature rapidly fell to normal. The total amount of sulfathiazole administered was 65 grams during a two-week period. (The drug was temporarily discontinued during the latter half of the first week of therapy.) The blood level at this time was 3.1 mg. per cent. The chest findings continued unchanged and indicated persisting consolidation of the left lower lobe.

During the evening of December 4, the seventeenth hospital day, it was noted that the urine was red in color. On the following morning the patient complained of marked weakness, and the temperature which had been normal for eight hours rapidly rose to 102° F. On examination, the patient was in poor condition and had a thready pulse with a rate of 130/min. He was markedly stuporous, barely responded to stimuli, and there was clear-cut jaundice of the skin and sclerae. The liver was tender and enlarged to two fingers'-breadth below the costal margin. The skin was cold and wet, and the respirations were shallow and 40/min. The urinalysis had been repeatedly negative except for an occasional one plus albumin. Now the urine showed three plus albumin and was reddish-brown in color. The benzidine test was strongly positive and bile was doubtfully positive. The sediment showed no formed elements. The blood count showed a hemoglobin of 30 per cent, erythrocytes 1,790,000, platelets 590,000, leukocytes 65,800 with neutrophiles 36 per cent, band forms 24 per cent, young forms 5 per cent, myelocytes 6 per cent, premyelocytes 3 per cent, plasma cells 4 per cent, lymphocytes 16 per cent and monocytes 6 per cent. The erythrocytes exhibited anisocytosis and a considerable amount of microspherocytosis. There were three nucleated red cells per hundred leukocytes. The icterus index was 37.5, the van den Bergh direct-immediate, and 1.5 mg. of bilirubin per 100 c.c. of serum. The blood urea nitrogen rose to 40 mg. per cent, and the non-protein nitrogen to 60 mg. per cent. No sulfathiazole was present in the blood.

An intravenous infusion of 5 per cent glucose in saline was begun, and arrangements were made for an immediate transfusion. The patient's blood showed marked autoagglutination upon typing. After thoroughly washing his red cells in saline, he was found to have type A (Landsteiner) blood. In crossmatching with prospective donors the same difficulty was encountered. The patient's plasma and serum agglutinated the red cells of all four blood types as shown in figure 1. In view of the critical condition of the patient, it was deemed advisable to transfuse him with Type A

TABLE I

	11/18	11/29–30	12/2–3	12/5	12/6	12/7	12/9	12/11	12/12–13	12/16–17	12/19–21	12/23–24	12/26–27	12/30	1/9
Blood															
Hemoglobin (Sahli) %	94	92	82	30	50	48	52	78		78	75		76		80
Hemoglobin, grams %	13.6	13.3	11.9	4.4	7.3	7.0	7.5	11.3		11.3	10.8		11.0		11.6
Erythrocytes, millions/cu. mm.	4.9	4.7	4.2	1.79	1.92	2.5	2.83	4.3		3.7	3.86		4.2		3.96
Nucleated red cells per cu. mm.	0	0	0	2,000	3,000	4,400	530			260	0		0		0
Leukocytes per cu. mm.	16,000	22,900	11,900	65,800	55,200	67,400	27,800	14,600		13,200	13,200		10,500		9,700
Neutrophiles %	56	86	83	36	42	61	68	75		59	59		65		63
Band Forms %	33	1	1	24	28	7	5	2		21	5		0		1
Young Forms %	0	0	0	5	8	10	8	1		0	0		0		0
Myelocytes %	0	0	0	6	6	5	8	0		0	0		0		0
Premyelocytes %	0	0	0	3	0	0	0	0		0	0		0		0
Lymphocytes %	7	9	9	16	7	13	8	14		15	28		29		33
Monocytes %	4	4	7	6	5	3	3	8		5	8		6		3
Plasma cells %	0	0	0	4	4	1	0	0		0	0		0		0
Reticulocytes %					1.9	2.8	11.2	4.0		1.4	0.8				
Platelets per cu. mm.				590,000		460,000	300,000				430,000		410,000		210,000
Mean corpuscular thickness, micr.					3.1				1.8						
Fragility test % saline				.42–.36											
Heterophilic antibody test							1:16								
Blood Chemistry															
Icteric index				37.5	26.3	15	8.9		5.8				12.0		
Van den Bergh: direct				immed.	biphasic	delayed	delayed		delayed						
Serum bilirubin, mg. %				1.5	1.0	0.6	0.4		0.25						
Urea nitrogen, mg. %	12.7			40.0	33.4	16.7	16.3	24.4	15.7				14.6		
Non-protein nitrogen, mg. %				60.0	61.2	31.2	38.9	54.6	38.7				35.9		
Cholesterol, mg. %					137.5			158.3					200.0		
Cholesterol esters, mg. %					75.8			100.0					125.0		
Total proteins, gm. %								5.34					6.29		
Albumin, gm. %								2.75					3.69		
Globulin, gm. %								2.59					1.84		
Fibrinogen, gm. %								0					0.76		
Sulfathiazole conc., mg. %		8	3.1	0											
Urine															
Appearance	clear		clear	red	red	sl. red	clear		clear	clear		clear			
Albumin	±		+	++	+++	+++	0		+	+		0			
Bile	0		0	±	0	0	0		0	0		0			
Benzidine				++++	++++	+	neg.		neg.	neg.		neg.			
Urobilinogen, dilution of serum					1:125		1:70		1:50						
Microscopic	neg.		neg.	neg.	2–4RBC 3–6WBC renal cells and casts.	debris	neg.		neg.	neg.		neg.			
Heller test for hgb.					pos.	pos.						neg.			
Miscellaneous															
Hippuric acid synthesis, gm.							1.0		1.0	1.65		2.12		1.5	2.79
Bromsulphalein test, 30 min.									55%		85%			5%	
Galactose tolerance test, gm.											2.46				
Spinal tap														neg.	
Spinal Wassermann														neg.	
Blood Wassermann and Kahn tests	+++		++++	++++											
Donath-Landsteiner test						neg.									
Cold (provocative) test										neg.		neg.			
Blood transfusions, c.c.				1,000	500	500	500								

blood slowly by the citrate method. He received 1,000 c.c. of citrated blood that day without reaction, and there was striking improvement in his general condition.

On the following day, December 6, there was much improvement in the general condition of the patient. The jaundice was less marked, and there was no drowsiness or stupor. The liver was now only one finger's-breadth below the costal margin. The urinary output was satisfactory. The laboratory findings (summarized in table 1) indicated a lessening of the anemia, decreasing jaundice, marked immaturity of the

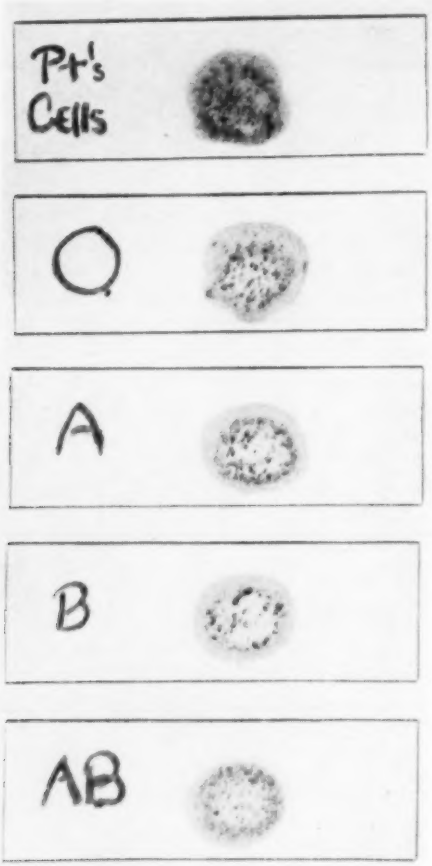

FIG. 1. Autoagglutination and panagglutination exhibited by the patient's serum.

erythrocytes and granulocytes, persistent hemoglobinuria, cellular evidence of renal damage, increased urobilinogen in the urine, and poor liver function. The Heller test (precipitation of blood-red stained urinary phosphates by means of alkali and heat) was positive and indicated the presence of hemoglobin in the urine. Spectroscopic examination was not done.

The patient received three more transfusions of 500 c.c. of citrated blood, the dates being December 6, 7, and 9. Autoagglutination and panagglutination were still present during the last crossmatchings on December 9, and persisted for several days thereafter. By that time the jaundice, hepatomegaly and hemoglobinuria were gone. There was

steady clinical improvement despite a fluctuating temperature and slowly resolving pneumonia. Tests of hepatic function, such as bromsulphalein, hippuric acid synthesis, blood cholesterol and proteins, showed significant changes. Even at the time of discharge on December 31, not all of these tests had returned to normal figures. The azotemia, however, had disappeared by this time. On December 12 the mean corpuscular thickness was normal and spherocytes were no longer seen.

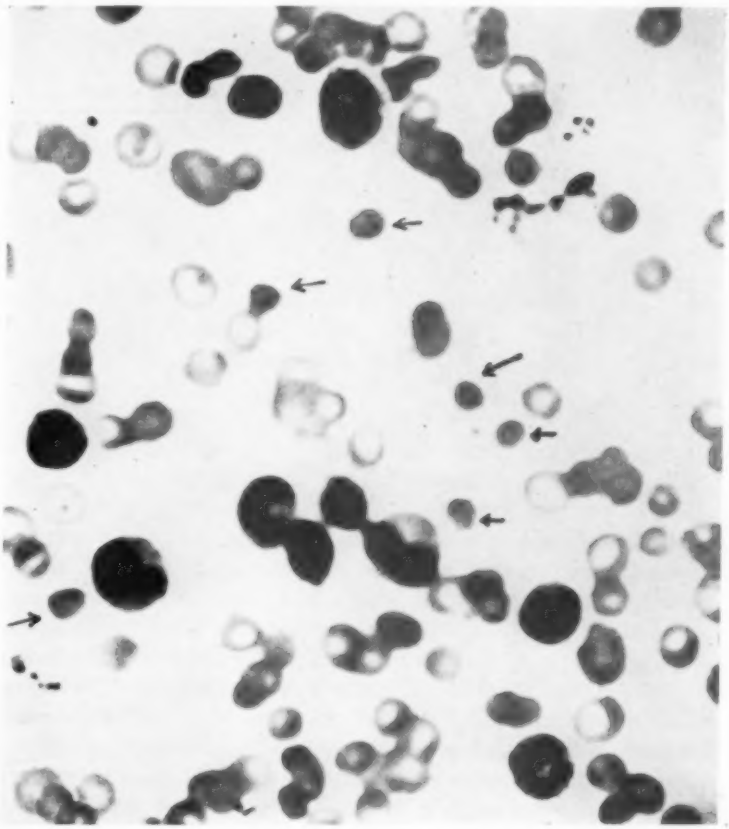

FIG. 2. Peripheral blood smear showing a number of microspherocytes.

On the day of discharge, December 31, the patient felt well, and although there was clinical and radiographic evidence of a small but definite area of unresolved pneumonia in the left lower lobe, the patient was discharged from the hospital.

The patient returned on January 9, 1941, for a check-up before going to a convalescent home. At this time, which was 35 days after the onset of the acute hemolytic episode, there was still a moderate anemia present despite continuous iron therapy. Examination of the lungs showed a patch of dullness, increased fremitus and bronchial breathing, though decreased in extent, at the inferior angle of the left scapula. The hippuric acid synthesis at this time was slightly below normal.

COMMENT

During the time that the patient's blood exhibited panagglutination the clumps of red blood cells on the blood typing and crossmatching slides could not be

broken up by the addition of a drop of physiological saline. Experiments were conducted with the patient's blood on December 5 to determine the titer of these agglutinins. Saline dilutions of the patient's serum were mixed on glass slides with suspensions of the patient's washed red cells, type O cells, type A cells and sheep cells. The agglutinins, however, were found to be present in low titer as complete agglutination occurred in all cases with 1:2 dilutions of serum and rouleaux formation with the 1:4 dilutions. Rabbit cells were agglutinated in a dilution of 1:128 but this was found to be due to a species agglutinin found in all types of human blood.

On December 9, the Donath-Landsteiner test was performed and was negative. The patient's serum of that day and a 5 per cent suspension of his washed red cells were then incubated in the serological test tube at 37° C. for 24 hours. No hemolysis occurred. The patient's packed washed red cells were kept under the same conditions in a 10 mg. per cent saline solution of the sulfathiazole he had received for treatment, and there was no hemolysis. When this concentration of sulfathiazole was produced experimentally in a sample of his serum and incubated in a similar manner with his packed washed red cells, there was no hemolysis. High concentrations of rabbit testing serum and the type VII antipneumococcus rabbit serum he had received for treatment were then produced in saline and in the patient's own serum. When these were placed in contact with the patient's packed washed red cells under like conditions, no hemolysis was noted. In other words, no autohemolysis could be demonstrated experimentally in vitro. Also, sulfathiazole and antipneumococcus type VII rabbit serum did not produce hemolysis of the patient's blood in vitro.

On two occasions a cold provocative test was done in which the patient's hands were immersed for 15 minutes in ice water at 5° C. All urine specimens were saved for the following nine hours, and there was no evidence of hemoglobinuria.

In reviewing this case, there are several interesting points which should be mentioned. There was a rapid satisfactory clinical response following the first administration of sulfathiazole. Within 48 hours the temperature had dropped to normal and the patient felt much improved. However, the pulmonary signs of consolidation were entirely unchanged in spite of this clinical improvement and resolution of the pneumonic process required several weeks. The toxic delirium or psychosis exhibited by the patient preceded the commencement of specific chemotherapy and it rapidly disappeared as the clinical condition improved, presumably as a result of sulfathiazole administration. It evidently was not an example of the occasional neurological or psychiatric manifestations incident to sulfonamide therapy. The chemotherapy was discontinued because of the suspicion of a drug fever, and the first indication of a toxic reaction was the red urine that the patient voided about 24 hours after the sulfathiazole therapy had been stopped. On the following day the hemolytic anemia was fully developed, and the blood at this time contained no sulfathiazole. The usual rapid excretion of sulfathiazole probably accounted for this. The fact that the first sign of the hemolytic anemia occurred 24 hours after the drug had been stopped may be explained as a delayed toxic reaction to the drug.

The laboratory findings pointing to acute hemolytic anemia were the red-colored urine which gave a strongly positive benzidine reaction and showed

few or no red blood cells, a positive urinary urobilinogen up to 1:125, erythrocytes which rapidly fell to 1,790,000 with 30 per cent hemoglobin, icterus index of 37.5, and a mean corpuscular thickness of 3.1 microns (normal range 1.7 to 2.5 microns). Laboratory evidence of toxic hepatitis as shown by impaired liver function was as follows: direct immediate van den Bergh which was transitory; hippuric acid synthesis in which less than one gram was excreted; bromsulphalein test showing as high as 85 per cent retention after 30 minutes; low blood cholesterol of 137.5 mg. per cent; diminished total protein of 5.34 mg. per cent with a 1:1 albumin-globulin ratio and no fibrinogen. Bile and urobilinogen were both present in the urine. There was the following laboratory evidence of renal damage: coarsely granular casts and renal parenchymal cells in the urine, and moderate azotemia, i.e., non-protein nitrogen 60 and urea nitrogen 40 mg. per cent. Certain laboratory findings pointed to marked bone marrow activity with regeneration. These were a leukocytosis reaching 67,400, nucleated red cells totaling 4,400, blood platelets 590,000, reticulocytes 11.2 per cent, and a marked shift to the left, myelocytes and premyelocytes being present in the differential.

Whereas the hemolytic process was of relatively short duration and the hematopoietic recovery was reasonably prompt, as judged by laboratory findings, the renal and, especially, the hepatic damage persisted long beyond the time one would expect from the reports of similar cases in the literature.

Discussion

In the reported cases of hemolytic anemia following sulfanilamide and sulfapyridine therapy, the association of syphilis with this complication has been pointed out. Syphilis is known to affect the hematopoietic system, as secondary anemia may develop in the secondary and tertiary stages of the disease. One must consider the possibility of syphilis causing some alteration of the blood possibly rendering the patient more susceptible to the development of acute hemolytic anemia, and at least two such fatal cases following sulfanilamide have been reported.[13] The serum of this patient gave persistently positive Wassermann and Kahn tests. The facts against this case being one of paroxysmal hemoglobinuria due to syphilis are that there was no previous history of hemoglobinuria when exposed to cold or at any time, that provocative tests when the patient's hands were kept in ice water were negative, and that the Donath-Landsteiner test was negative.

Another interesting feature of this case was the appearance of the acute hemolytic anemia after the first week of sulfathiazole therapy. In fact, it appeared at the end of the second week. Even if one were to take into account the few days that the drug was not given, the anemia began one day after the second course of treatment which lasted eight days. Acute hemolytic anemia following sulfanilamide and sulfapyridine administration has been shown to occur generally during the first to fifth days of treatment and, as a rule, not later than one week after the onset of therapy.[3] Here the anemia developed 15 days after the original administration of sulfathiazole and nine days after the beginning of the second course of therapy.

In 1938, Dameshek and Schwartz [15] produced acute hemolytic anemias in experimental animals by the injection of heterophilic hemolytic serum. When

moderate doses were used, they were able to create acute hemolytic anemia with spherocytosis. This work has recently been confirmed.[14] Since spherocytosis is found largely in congenital hemolytic icterus, in which condition there is assumed to be a primary defect in the red cell, the report of other diseases or conditions in which spherocytosis is seen to occur would add to our present incomplete knowledge of this phenomenon. For these reasons spherocytosis was looked for and found in this case, and was corroborated by a mean corpuscular thickness which was above normal. The fragility test, however, was normal. In regard to this, it has been found that in atypical acquired hemolytic anemias there may be normal red cell fragility associated with spherocytosis and, also, increased fragility without spherocytosis. Further investigation would seem to be indicated along these lines in acquired hemolytic anemias due to sulfonamide therapy or other causes. It would be interesting to see if spherocytosis could be found in such cases and whether it would be associated with hemolysins in the blood. No hemolysins could be demonstrated in this case by the methods employed. Autoagglutination which frequently is seen in acute hemolytic anemia and in a variety of other conditions may or may not be associated with demonstrable hemolysins in the blood.

The marked leukocytosis with extreme shift to the left in this case might be termed a leukemoid reaction, although considerably higher leukocyte counts have been reported in reactions following sulfonamide therapy. Leukemoid reactions may occur alone and independently of other complications. They may be due to either of two other factors, acute hemolytic anemia or toxic hepatitis, which coexisted in this patient.

The jaundice in this case was due to the combination of acute hemolytic anemia and toxic hepatitis. The normal liver can excrete all the bilirubin brought to it and only the most extreme hemolysis will in itself produce jaundice.[16] A reason for this is that a hemolytic process of such a degree must inevitably lead to decreased excretory power of the liver from anoxemia alone. When jaundice results from excessive production of bilirubin, as in hemolytic anemia, there must be a simultaneous increase in the hepatic load and decrease in hepatic function; and definite, prolonged poor liver function was present in this case.

The pathogenesis of renal damage in the course of sulfonamide administration may be divided theoretically into three types: (1) renal damage resulting from direct toxic effect of the drug on the kidney parenchyma (that such a process occurs from therapeutic doses has not been proved[17]); (2) renal damage from the deposition of sulfonamide drugs or their derivatives in the kidney tubules, pelvis or ureters. (This has been reported frequently with sulfapyridine and sulfathiazole.[3, 18] The very slight microscopic hematuria and the absence of crystals in our case indicate that deposition of sulfathiazole or acetylsulfathiazole was probably not the basis of the renal damage); (3) renal damage from the deposition of hemoglobin or its derivatives in the tubules with blockage. This process which results from severe hemolysis as, for example, the reaction following transfusion of incompatible blood, was the most probable cause of the renal damage in the case presented. Ravid and Chesner,[7] in their report of a fatal case of acute hemolytic anemia following sulfapyridine with autopsy, presented gross and microscopic corroboration of this process.

Conclusion

We have presented and discussed a case of acute hemolytic anemia, autoagglutination, leukemoid reaction, toxic hepatitis and renal damage following sulfathiazole therapy for a pneumococcus type VII lobar pneumonia in a man of 45, with recovery.

BIBLIOGRAPHY

1. Harvey, A. M., and Janeway, C. A.: The development of acute hemolytic anemia during the administration of sulfanilamide, Jr. Am. Med. Assoc., 1937, cix, 12.
2. Long, P. H., Bliss, E. A., and Feinstone, W. H.: Mode of action, clinical use and toxic manifestations of sulfanilamide: further observations, Jr. Am. Med. Assoc., 1939, cxii, 115.
3. Long, P. H., Haviland, J. W., Edwards, L. B., and Bliss, E. A.: The toxic manifestations of sulfanilamide and its derivatives, Jr. Am. Med. Assoc., 1940, cxv, 364.
4. Bannick, E. G., Brown, A. E., and Foster, F. P.: The therapeutic effectiveness and toxicity of sulfanilamide, Jr. Am. Med. Assoc., 1938, cxi, 770.
5. Antopol, W., Applebaum, I., and Goldman, L.: Acute hemolytic anemia with autoagglutination following sulfanilamide therapy: two cases, Jr. Am. Med. Assoc., 1939, cxiii, 488.
6. Spring, M., and Bernstein, I.: The coexistence of toxic hepatitis, acute hemolytic anemia and renal damage following sulfanilamide therapy; report of two cases, Ann. Int. Med., 1940, xiv, 153.
7. Ravid, J. M., and Chesner, C.: Fatal case of (hemolytic) anemia and nephrotic uremia following sulfapyridine administration, Am. Jr. Med. Sci., 1940, cxcix, 380.
8. Fosbinder, R. I., and Walter, L. A.: Sulfanilamide derivatives of heterocyclic amines, Jr. Am. Chem. Soc., 1939, lxi, 2032.
9. Lott, W. A., and Bergeim, F. H.: 2(p-aminobenzenesulfonamide) thiazole; a new chemotherapeutic agent, Jr. Am. Chem. Soc., 1939, lxi, 3593.
10. Van Dyke, H. B., Greep, R. O., Rake, G., and McKee, C. M.: Observations on the pharmacology of sulfathiazole and sulfapyridine, Proc. Soc. Exper. Biol. and Med., 1939, xlii, 410.
11. McKee, C. M., Rake, G., Greep, R. O., and Van Dyke, H. B.: Therapeutic effect of sulfathiazole and sulfapyridine, Proc. Soc. Exper. Biol. and Med., 1939, xlii, 417.
12. Schnitker, M. A.: Sulfanilamide and the negro (hemolytic anemia following therapy), Ohio State Med. Jr., 1939, xxxv, 1204.
13. Koletsky, S.: Fatal hemolytic anemia following administration of sulfanilamide, Jr. Am. Med. Assoc., 1939, cxiii, 291.
14. Tigertt, W. D., and Duncan, C. N.: Erythrocyte morphology in experimental hemolytic anemia as induced by specific hemolysin, Am. Jr. Med. Sci., 1940, cc, 173.
15. Dameshek, W., and Schwartz, S. O.: Hemolysins as the cause of clinical and experimental hemolytic anemias, Am. Jr. Med. Sci., 1938, cxcvi, 769.
16. Rich, A.: Pathogenesis of forms of jaundice, Bull. Johns Hopkins Hosp., 1930, xlvii, 338.
17. Molitor, H., and Robinson, H.: Some pharmacological and toxicological properties of sulfanilamide and benzyl sulfanilamide, Jr. Pharm. and Exper. Therap., 1939, xlv, 405.
18. Pepper, D. S., and Horack, H. M.: Crystalline concretions in renal tubules following sulfathiazole therapy, Am. Jr. Med. Sci., 1940, cxcix, 674.
19. Long, P. H.: Thiazole derivatives of sulfanilamide, Jr. Am. Med. Assoc., 1940, cxiv, 870.
20. Reinhold, J. G., Flippen, H. F., and Schwartz, L.: Toxicology of sulfathiazole in man, Am. Jr. Med. Sci., 1940, cxcix, 393.

21. FLIPPEN, H. F., SCHWARTZ, L., and ROSE, S. B.: Comparative effectiveness and toxicity of sulfathiazole and sulfapyridine in pneumococcic pneumonia, ANN. INT. MED., 1940, xiii, 2038.

22. BLAKE, F. G.: The treatment of pneumococcal pneumonia, New England Jr. Med., 1940, ccxxiii, 661.

23. CUTTS, M., BURGESS, A. M., and CHAFFE, F. H.: The treatment of lobar pneumonia with sulfathiazole and sulfapyridine, New England Jr. Med., 1940, ccxxiii, 762.

HYPERPARATHYROIDISM IN A PATIENT WITH ACROMEGALY *

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HYPERPARATHYROIDISM

THE parathyroids were first described as independent organs by Sandstrom [1] in 1880, but their function remained in doubt until 1896 when it was demonstrated [2] that their removal produced tetany. In 1909 MacCallum and Voegtlin [3] showed that the tetany of parathyroid insufficiency was associated with a fall in serum calcium and a rise in serum phosphorus.

In 1891, von Recklinghausen [4] described the anatomic syndrome of osteitis fibrosa cystica, distinguishing it from osteomalacia. Some years later, Erdheim [5] suggested that parathyroid enlargement found in association with osteitis fibrosa cystica was secondary to the bone changes. However, in 1926 Mandl [6, 7] found that parathyroid transplants were not affected by the bone changes in a patient with von Recklinghausen's disease, whereas the removal of a parathyroid tumor which was found in this patient was followed by clinical improvement. This suggested that the tumor was the underlying cause of the osseous changes. This relationship between von Recklinghausen's disease and the parathyroids was confirmed by Hannon and his co-workers [8] in 1926, Gold [9] in 1928, as well as Barr, Bulger and Dixon in 1929.[10, 11] The latter group, along with Wilder [12] and Snapper,[13] regarded hyperparathyroidism as a distinct clinical entity. Since then many reports have been published establishing the relationship of hyperparathyroidism to osteitis fibrosa cystica. Experimental evidence of the primary rôle played by the parathyroid hyperactivity has also been furnished by Jaffe, Bodansky and Blair.[14, 15, 16]

The observations of MacCallum and Voegtlin,[3] from which they concluded that the symptoms following parathyroidectomy were due to calcium deficiency, were confirmed and amplified by Luckhardt and Goldberg,[17] Salvesen,[18] and Collip.[19] With the isolation of a potent parathyroid extract by Hanson [20] and by Collip,[19, 21] and its administration in animals, disorders of calcium and phosphorus metabolism could be produced comparable to the picture in hyperparathyroidism.[38, 39]

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Investigators agree that the chief rôle of the parathyroid hormone consists of its important influence upon the metabolism of calcium and phosphorus. The injection of parathyroid extract-Collip produced four cardinal effects [22]: (1) rise in serum calcium, (2) rise in urinary calcium excretion, (3) fall in serum phosphorus, and (4) rise in urinary phosphorus excretion.

Aside from the bone changes in von Recklinghausen's disease, other clinical and chemical alterations have been repeatedly noted. These were well summarized by Albright, Aub and Bauer.[23] The clinical picture in its entirety presents features caused by (*a*) the hypercalcemia, such as weakness, lassitude, hypotonia and chronic constipation; (*b*) symptoms related to the skeletal system, such as bone pain and deformities, cysts of long bones and skull, spontaneous

FIG. 1. Face shows prominent malar processes, overhanging supraorbital ridges, broad nose, thick lips and large ears.

fractures, kyphosis and scoliosis; and (c) symptoms due to the transportation and excretion of calcium, such as polyuria, polydipsia, enuresis, nocturia, dysuria and renal calculi. There is also a constant increase in the plasma phosphatase in active cases of hyperparathyroidism.[24]

ACROMEGALY

Our present knowledge of acromegaly dates back to 1886 when Pierre Marie,[25] in reporting two cases of this condition, suggested that it was a disease entity associated with the pituitary gland. He was the first to apply the name acromegaly to the clinical picture. However, Marie believed the condition to be the result of either hypofunction or dysfunction of the gland, and it remained for Minkowski [26] in 1887 to postulate hyperactivity of the pituitary as the responsible mechanism. This was verified by Benda [27] in 1900 when he found a constant relationship of eosinophilic adenomata with acromegaly. Cushing [28] then offered

experimental proof of the association of skeletal growth to the pituitary. In 1929, Putnam and his associates [29] produced acromegaly in dogs by the injection of anterior lobe extracts.

The clinical picture of acromegaly is well known. The disease is characterized by the onset in early adult life of skeletal, cutaneous and visceral changes.

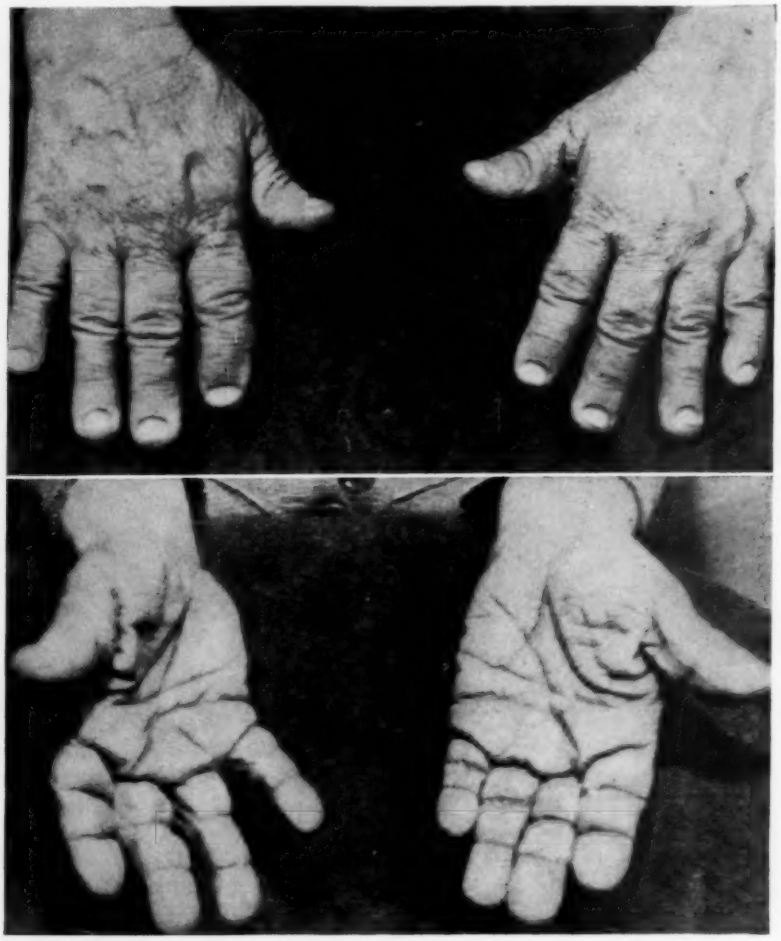

FIG. 2. Hands show spading and loose, wrinkled, inelastic skin.

There are increased dimensions of the hands and feet; broad palms and thick fingers producing a spade-like appearance; tufting of the tips of the distal phalanges, with hooking of the terminal phalanges of the thumbs; overgrowth of the bones of the face particularly involving the mandible, supraorbital ridges and nasal bones; enlarged frontal sinuses; massive protruding jaw (prognathism); widely spaced teeth; changes in the vertebrae resulting in kyphosis; wrinkled and thickened skin; hypertrichosis; gonadal hypertrophy with eventual atrophy and loss of libido; splanchnomegaly; thick tongue; glycosuria and hyper-

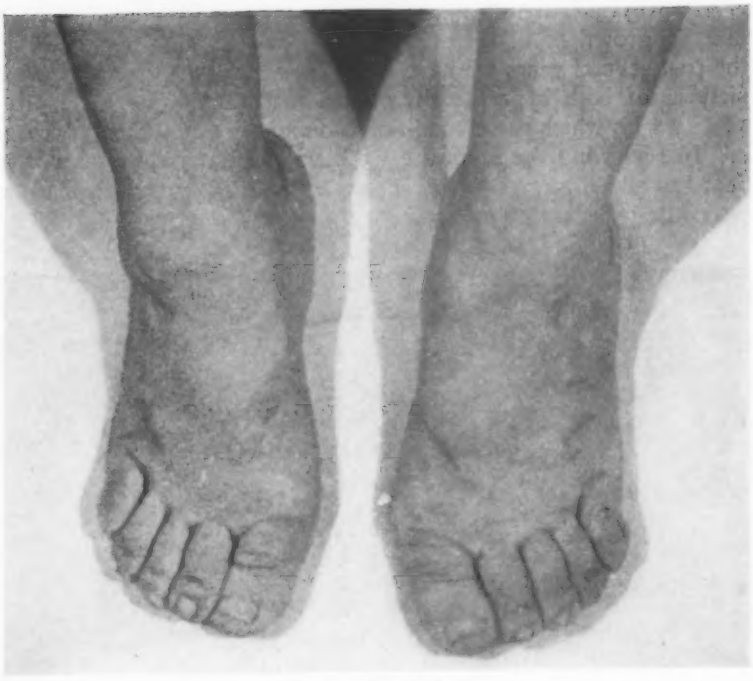

FIG. 3. Spade feet.

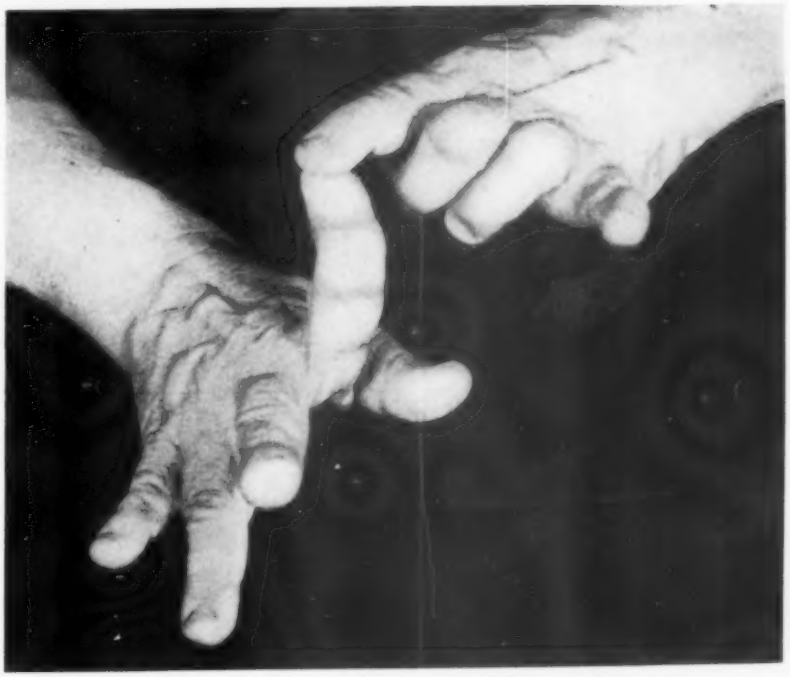

FIG. 4. Demonstrating the marked hypotonia.

glycemia. The thyroid, thymus, parathyroids or adrenals may show hypertrophy or adenomatous growths.

For the past several years we have been observing a patient who presents the clinical pictures of both hyperparathyroidism and acromegaly. Because of the apparent rarity with which these conditions co-exist, we consider this case worthy of report. In reviewing the literature we have encountered no similar instance. This patient has added interest because she seems to suggest a probable relationship between the pituitary and the parathyroid glands.

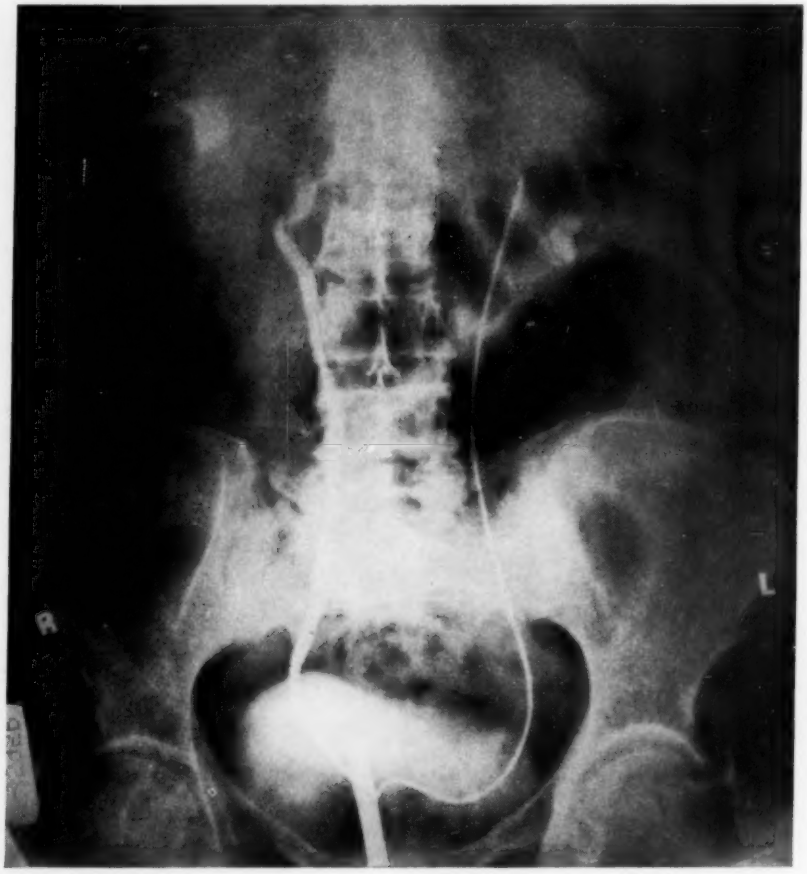

FIG. 5. A large calculus fills the pelvis of the right kidney. Several calculi are seen in the lower pole of the left kidney.

CASE REPORT

On May 26, 1936, Mrs. F. D., aged 68, was admitted to the Beth Israel Hospital. In 1924 she had had a radical mastectomy because of a lump in her right breast. The remainder of her past history was irrelevant until 1928 when she was struck on the head by a heavy piece of baggage. One month later she began to be troubled with severe parietal headaches. At this time she became aware of the fact that her hands were becoming large and clumsy and her features coarse.

It was not these changes in her appearance but recurrent urinary symptoms that were responsible for her hospitalization. Since 1928 she had been troubled with pain in the right lumbar region, occasionally radiating to the groin. In 1932 she was institutionalized elsewhere because of frank hematuria. Roentgen-rays taken at that time revealed right renal calculi. In 1935 there was a recurrence of the urinary bleeding along with left lumbar pain. Thereafter lumbar pain and hematuria recurred at frequent intervals. Three months prior to her admission to the Beth Israel Hospital roentgen-rays taken elsewhere showed bilateral renal calculi. For three years she had known that her blood pressure was high. For two years she had been troubled with obstinate constipation, weakness, headaches and occasional dizzy spells.

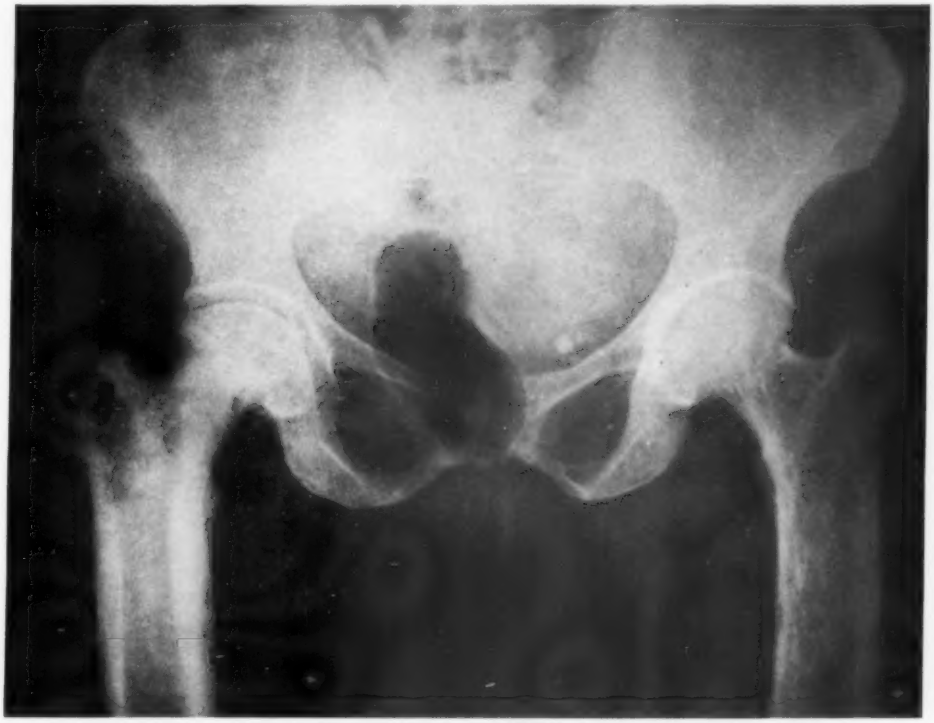

FIG. 6. The pelvis shows extensive areas of osteoporosis involving the iliac bones and coarsening of the structure in the cancellated bone. The cortex of the right femur is markedly thickened and there are numerous small cyst formations in the head and the trochanter.

Physical examination showed a well preserved elderly woman with acromegalic features. She had prominent malar processes, overhanging supraorbital ridges, a broad nose, large lips and ears, and some prognathism (figure 1). There was slight concentric narrowing of the visual fields. The thyroid gland was not enlarged. Soft systolic murmurs were heard over the apex and aortic areas. The blood pressure was 160 mm. Hg systolic and 96 mm. diastolic. A mass was felt in the right flank. She had "spade" hands and wide feet (figures 2 and 3). There was diffuse pigmentation of the skin with some pigmented nodules on the face. A very striking feature was the marked hypotonia of the fingers (figure 4).

Laboratory studies showed urine which concentrated to 1.020 with one plus albumin and many red and white cells. A sugar tolerance test showed a maintained high

level with 200 mg. of glucose per 100 c.c. of blood after three hours. At two and three hours there were traces of sugar in the urine. The blood Wassermann test was negative. The blood non-protein nitrogen varied from 39 to 50 mg. per cent. The blood count was normal. Repeated basal metabolic tests were within normal limits.

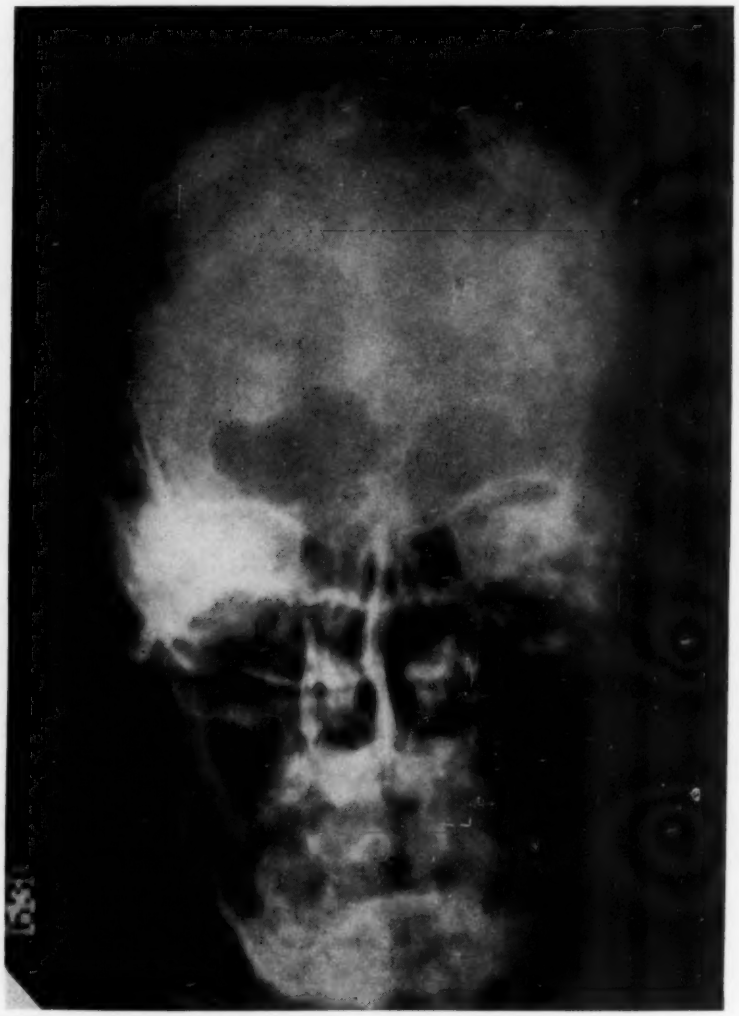

FIG. 7. Roentgen-ray studies of the skull show diffuse osteoporotic changes and numerous areas of hyperostosis. The sinuses are enormously enlarged.

FIG. 7. Roentgen-ray studies of the skull show diffuse osteoporotic changes and numerous the pelvis of the right kidney and calcareous deposits in the lower pole of the left kidney (figure 5).

Because of the renal calculi, marked hypotonia, constipation and weakness a clinical diagnosis of hyperparathyroidism was made. Further studies were undertaken in an effort to substantiate this impression.

Blood studies on three occasions showed an average serum calcium of 13.7 mg., and a serum phosphorus of 3.8 mg. per 100 c.c. of blood. Plasma phosphatase was 8.4 Bodansky units, the normal for adults being 2 to 3.5 units. Efforts to determine her calcium balance were inconclusive.

The roentgen-ray studies of the skeletal system showed changes in the pelvic girdle, skull, long bones and vertebrae. The pelvis (figure 6) showed extensive areas of osteoporosis involving the iliac bones, in each of which large cyst-like areas were present. There was coarsening of the structure of the cancellated bone. The most

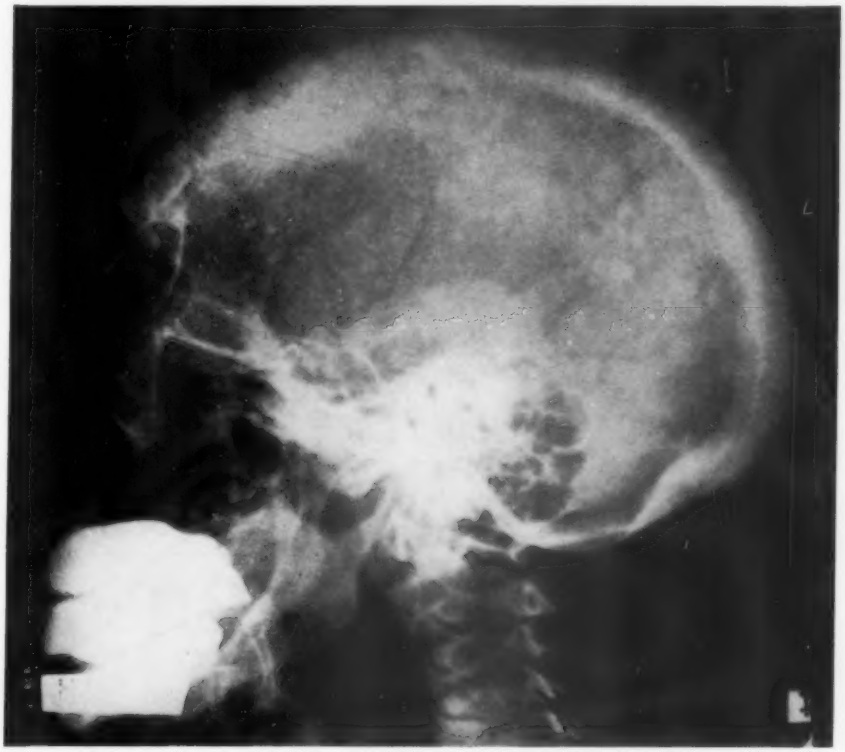

FIG. 8. The lateral view of the skull shows marked widening of the diploetic layer which is occupied by coarse trabeculated bone. In the upper part of the frontal bone there is a large area of hyperostosis extending inward from the inner table. The vascular grooves are markedly deepened. The mastoid cells are enlarged. The sella turcica is markedly enlarged and the clinoids pneumatized.

pronounced changes were found in the skull (figures 7 and 8). Here diffuse osteoporotic changes and numerous areas of hyperostosis were present. The diploetic layer was markedly widened. In the upper part of the frontal bone there was a large area of hyperostosis extending inward from the inner table. The vascular grooves were deepened. The sinuses and mastoid cells were enormously enlarged. There was also marked enlargement of the sella turcica with pneumatization of the clinoids. All of the long bones showed extensive osteoporotic changes (figure 9). In addition, in several of them definite cyst formation could be demonstrated. These changes were marked in the right femur (figure 6) where there was also marked thickening of the cortex. The hands and feet (figures 10 and 11) showed characteristic tufting of

the terminal phalanges with hooking of the terminal phalanges of the thumbs. The widening of the phalangeal bases and slender shafts were particularly pronounced in the feet.

The hematuria gradually subsided and the patient was discharged after a seven week stay in the hospital. She was admitted a second time in July 1937 because of bleeding hemorrhoids and a severe anemia which necessitated two transfusions.

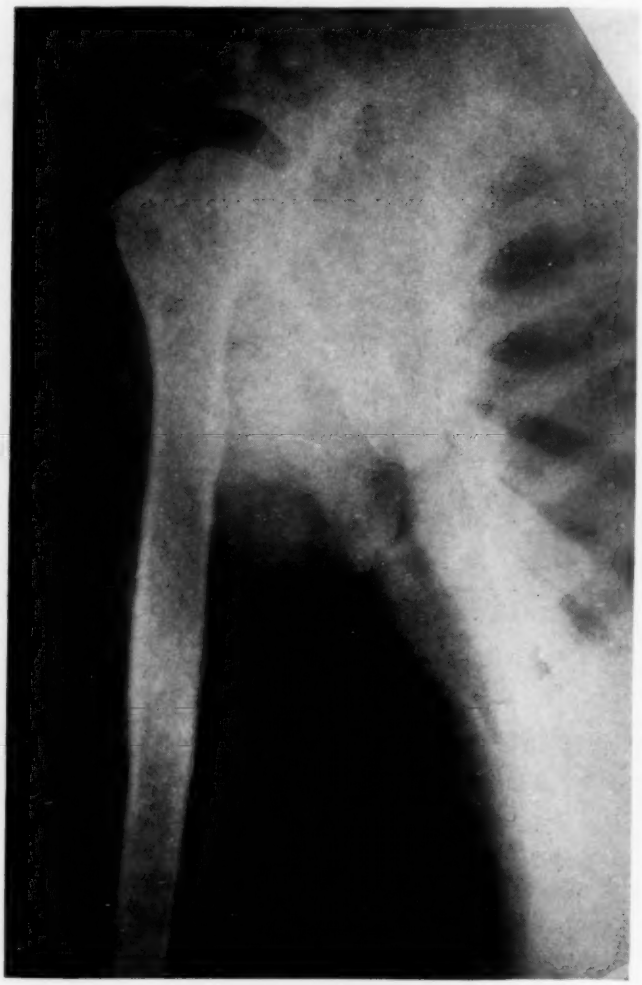

FIG. 9. Roentgen-ray of the humerus shows osteoporotic changes and cyst formations similar to those seen in all the long bones. The ribs show diffuse lamellation and irregularity in outline due to disappearance of cortical bone and increase in cancellated tissue.

Her third admission, for recurring hematuria, occurred in June of 1938. Physical examination and renal findings were essentially the same as on her first admission. Blood studies now showed serum calcium of 11.8 mg., serum phosphorus of 3.5 mg., and plasma phosphatase 16.6 Bodansky units. Because the renal involvement was bilateral and the function of the right kidney impaired, surgical intervention was

deemed inadvisable. When the hematuria had subsided she was discharged. On her fourth admission, in August 1940, the chemical and roentgen-ray findings were essentially unchanged.

Discussion

We have no way of knowing at present whether this patient has hyperplasia or adenoma of the parathyroid gland. Hyperparathyroidism is believed by many investigators to be a primary disturbance of the parathyroids. However, in this

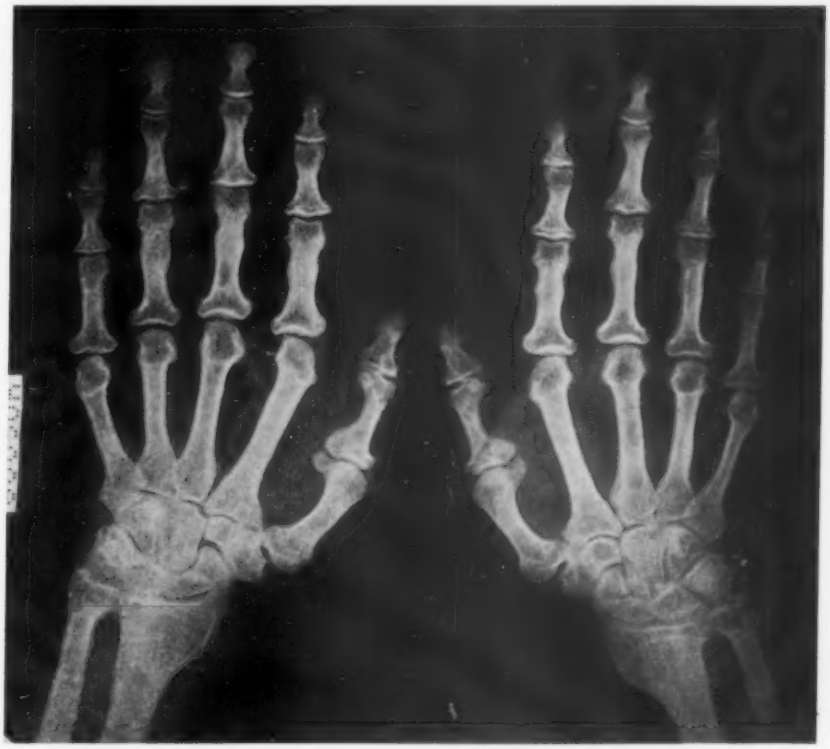

Fig. 10. Roentgen-rays of the hands show marked thickening of the soft tissues so that the fingers are club-like in character. There is tufting of the terminal phalanges with hooking of the terminal phalanges of the thumbs.

case there arises the question of the relationship of the hyperparathyroidism to the acromegaly which apparently antedated it. Several possibilities may be suggested:

1. It is, of course, quite possible that we are here dealing with the coincidental existence of two distinct and unrelated disease entities.

2. Knowing that hyperplasia of many organs including endocrine glands may be found in patients with acromegaly, a fact which was demonstrated by Cushing and Davidoff,[30] the possibility of such hyperplasia resulting in clinical hyperfunction must be considered.

3. We must also bear in mind the frequency with which adenomata of the various endocrine glands exist in acromegaly. In fact, Davidoff [31] refers to acromegaly as a syndrome with multiple adenomatosis.

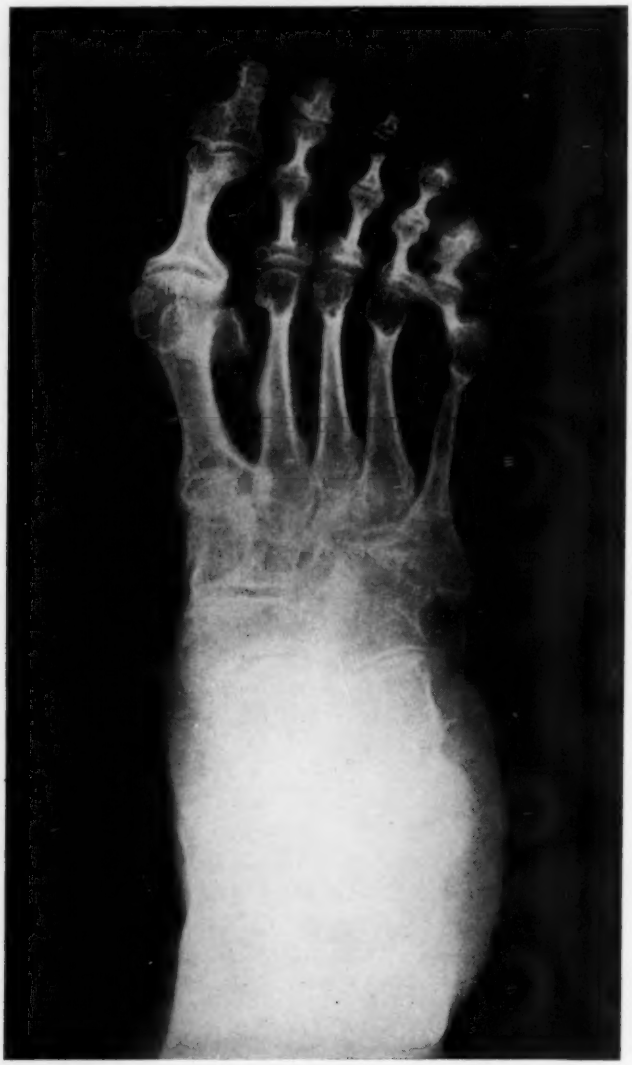

FIG. 11. Roentgen-rays of the feet show changes similar to those seen in the hands. The shafts of the phalanges are very slender and their bases markedly widened.

4. There is the possibility that a parathyrotropic substance elaborated in the pituitary may be responsible for the hyperparathyroidism. Hertz and Albright [32] injected the urine of a patient with pituitary hyperplasia into rabbits, causing hyperplasia of their parathyroids. This suggested that a parathyrotropic substance was present, which could have originated only in the pituitary gland.

Whether the parathyroid hyperplasia or adenomata previously referred to are caused by such parathyrotropic substance or by the growth factor of the anterior lobe is not clear. Hertz and Kranes [33] have produced hypertrophy of the parathyroid cells by the injection of an extract of the anterior lobe of the pituitary. Hoffman and Anselmino [34] found histologic evidence of parathyroid hyperplasia following administration of pituitary extracts, although the total volume of the gland was not increased. In addition, they demonstrated an elevation of the serum calcium similar to that produced by parathormone administration.

Although Aschner [35] and Collip [36] found no changes in the parathyroids of hypophysectomized animals, Smith [37] reported definite atrophy. While the bulk of experimental work seems to point definitely to a pituitary influence on the activity of the parathyroid gland, there is no conclusive evidence of the existence of a parathyrotropic factor.[40]

Conclusions

A case of hyperparathyroidism in a patient with acromegaly is presented. The development of our knowledge of each of these conditions and its clinical picture are briefly reviewed. The possibilities of relationship of the von Recklinghausen syndrome to the acromegaly are considered.

BIBLIOGRAPHY

1. Sandstrom, I.: A new gland in the oesophagus, Upsala läkaref. förh., 1880, xv, 441–471.
2. Vassale, G., and Generali, F.: Results of parathyroidectomy, Arch. ital. de biol., 1896, xxv, 459–464.
3. MacCallum, W. G., and Voegtlin, C.: On the relation of tetany to the parathyroid glands and to calcium metabolism, Jr. Exper. Med., 1909, xi, 118–151.
4. von Recklinghausen, F.: Fibrous or deforming osteitis, osteomalacia and osteoplastic carcinosis in their relationship to each other, Festschr. Rudolf Virchow, Berlin, 1891, 1–89.
5. Erdheim, J.: Parathyroid findings in osteomalacia, Sitzungsb. d. k. Akad. d. Wissensch., Math.-Naturw. Klasse, 1907, cxvi, sect. 3, 311–370.
6. Mandl, F.: Treatment of localized and generalized fibrous osteitis, Wien. klin. Wchnschr., 1926, xxxix, 1046–1048.
7. Mandl, F.: Attempt to treat generalized fibrous osteitis by extirpation of parathyroid tumor, Zentralbl. f. Chir., 1926, liii, 260–264.
8. Hannon, R. R., Shorr, E., McClellan, W. S., and DuBois, E. F.: Case of osteitis fibrosa cystica (osteomalacia?) with evidence of hyperactivity of parathyroid bodies; metabolic study, Jr. Clin. Invest., 1930, viii, 215–227.
9. Gold, E.: The significance of parathyroid enlargement in the generalized osteitis fibrosa of Recklinghausen, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1928, xli, 63–82.
10. Barr, D. P., Bulger, H. A., and Dixon, H. H.: Hyperparathyroidism, Jr. Am. Med. Assoc., 1929, xcii, 951–952.
11. Barr, D. P., and Bulger, H. A.: Clinical syndrome of hyperparathyroidism, Am. Jr. Med. Sci., clxxix, 449–476.
12. Wilder, R. M.: Hyperparathyroidism; tumor of parathyroid glands associated with osteitis fibrosa, Endocrinology, 1929, xiii, 231–244.
13. Snapper, I.: Tumor of accessory thyroid and bone deformities, Nederl. tijdschr. v. geneesk., 1929, ii, 4758–4773.

SNAPPER, I.: Parathyroid tumor and changes of bones, Arch. Int. Med., 1930, xlvi, 506–523.

14. JAFFE, H. L., BODANSKY, A., and BLAIR, J. E.: Fibrous osteodystrophy (osteitis fibrosa) in experimental hyperparathyroidism of guinea pigs, Arch. Path., 1931, xi, 207–228.
15. BODANSKY, A., BLAIR, J. E., and JAFFE, H. L.: Experimental hyperparathyroidism in guinea pigs leading to osteitis fibrosa, Jr. Biol. Chem., 1930, lxxxviii, 629–647.
16. BODANSKY, A., and JAFFE, H. L.: Parathormone dosage and serum calcium and phosphorus in experimental chronic hyperparathyroidism leading to osteitis fibrosa, Jr. Exper. Med., 1931, liii, 591–604.
17. LUCKHARDT, A. B., and GOLDBERG, B.: Preservation of the life of completely parathyroidectomized dogs by means of the oral administration of calcium lactate, Jr. Am. Med. Assoc., 1923, lxxx, 79–80.
18. SALVESEN, H. A.: The function of the parathyroids, Jr. Biol. Chem., 1923, lvi, 443–456.
19. COLLIP, J. B.: The extraction of a parathyroid hormone which will prevent or control parathyroid tetany and which regulates the level of blood calcium, Jr. Biol. Chem., 1925, lxiii, 395–438.
20. HANSON, A. M.: The hydrochloric X of the bovine parathyroid and its phosphotungstic acid precipitate, Mil. Surgeon, 1924, liv, 76–81.

HANSON, A. M.: Parathyroid preparations, Mil. Surgeon, 1924, liv, 554–560.

21. COLLIP, J. B., and CLARK, E. P.: Further studies on the physiological action of a parathyroid hormone, Jr. Biol. Chem., 1925, lxiv, 485–507.
22. LISSER, H., and SHEPARDSON, H. C.: Parathyroids; function of parathyroid glandules, The Cyclopedia of Medicine, 1934, F. A. Davis Co., Philadelphia, ix, 656–685.
23. ALBRIGHT, F., AUB, J. C., and BAUER, W.: Hyperparathyroidism; common and polymorphic condition as illustrated by seventeen proved cases from one clinic, Jr. Am. Med. Assoc., 1934, cii, 1276–1287.
24. KAY, H. D.: Plasma phosphatase; enzyme in disease, particularly in bone disease, Jr. Biol. Chem., 1930, lxxxix, 249–266.
25. MARIE, P.: Two cases of acromegaly with especial hypertrophy of the upper and lower extremities and head, Rev. de méd. Par., 1886, vi, 297–333.
26. MINKOWSKI, O.: cited by WERNER, A. A.: Endocrinology, clinical application and treatment, 1937, Lea and Febiger, Philadelphia, p. 102.
27. BENDA, C.: Normal structure and several pathological changes of the human pituitary, Arch. f. Anat. u. Physiol., Physiol. Abt., 1900, xxiv, 373–380.
28. CUSHING, H.: Dyspituitarism, Harvey Lectures, 1910–1911, 31–45.
29. PUTNAM, T. J., BENEDICT, E. B., and TEEL, H. M.: Studies in acromegaly; experimental canine acromegaly produced by injection of anterior lobe pituitary extract, Arch. Surg., 1929, xviii, 1708–1736.
30. CUSHING, H., and DAVIDOFF, L. M.: The pathological findings in four autopsied cases of acromegaly with a discussion of their significance, The Rockefeller Inst. for Med. Res., N. Y., 1927, monograph no. 22.
31. DAVIDOFF, L. M.: Hyperpituitarism and hypopituitarism, Bull. New York Acad. Med., 1940, xvi, 227–243.
32. HERTZ, S., and ALBRIGHT, F.: The demonstration of a parathyreotropic substance in the urine of patients with hyperparathyroidism due to diffuse hyperplasia of all parathyroid glands, Jr. Clin. Invest., 1934, xiii, 698.
33. HERTZ, S., and KRANES, A.: Parathyreotropic action of anterior pituitary: histologic evidence in rabbit, Endocrinology, 1934, xviii, 350–360.
34. HOFFMAN, F., and ANSELMINO, K. J.: The effect of anterior pituitary extracts on blood calcium level, Klin. Wchnschr., 1934, xiii, 44–45.
35. ASCHNER, B.: The function of the pituitary, Arch. f. d. ges. Physiol., 1912, cxlvi, 1–146.

36. COLLIP, J. B.: Diabetogenic, thyrotropic, adrenotropic and parathyrotropic factors of pituitary, Jr. Am. Med. Assoc., 1935, civ, 916–921.
37. SMITH, P. E.: Disabilities caused by hypophysectomy and their repair; tuberal (hypothalamic) syndrome in rat, Jr. Am. Med. Assoc., 1927, lxxxviii, 158–161.
38. GREENWALD, I., and GROSS, J.: Effect of long continued administration of parathyroid extract upon excretion of phosphorus and calcium, Jr. Biol. Chem., 1926, lxviii, 325–333.
39. ALBRIGHT, F., and ELLSWORTH, R.: Studies on physiology of parathyroid glands; calcium and phosphorus studies on case of idiopathic hypoparathyroidism, Jr. Clin. Invest., 1929, vii, 183–201.
40. COLLIP, J. B.: Corticotropic (adrenotropic), thyrotropic and parathyrotropic factors, Jr. Am. Med. Assoc., 1940, cxv, 2073–2079.

EDITORIAL

HYPERCALCEMIA AND RENAL INJURY

It is well known that with skeletal immobilization there occurs bone rarefaction. It is also well known that a considerable portion of the lime salts exported from the body in this process are handled by the kidneys. The excess excretion of calcium in the urine, or hypercalciuria, is presumably the reason for the frequency of urinary tract stones in patients with healing fractures, an association which has been observed for many years.

That hypercalcemia can be a direct result of the rapid mobilization of lime salts during the development of atrophy of disuse has only very recently been suggested. Two years ago, following an attack of poliomyelitis, a young patient of Dr. William Orr's, in Buffalo, developed renal insufficiency; and, associated with the usual chemical findings in the serum of uremia, there was repeatedly observed a high serum calcium.[1] It was independently suggested by Dr. Fuller Albright of Boston and Dr. E. A. Park of Baltimore that the hypercalcemia might be due to the rapid mobilization of lime salts from disuse atrophy, and that the hypercalcemia per se might have caused damage to the renal tubules with resulting uremia.

Orr followed up this lead and examined the serum calcium in 11 cases of poliomyelitis in the paralytic stage, finding hypercalcemia in 10 of them.[1] Wilkins [2] also found serum calcium elevations in some of the paralytic cases he examined at the Children's Hospital School with this point in mind.

With this background workers were on the alert for a syndrome of renal damage in association with extensive skeletal immobilization. Last spring Albright and his colleagues at the Massachusetts General Hospital reported [3] the case of a 14-year-old boy who, while in an extensive body cast for a fractured femur, developed signs and symptoms of severe renal damage. Hypercalcemia, hypercalciuria, albuminuria, inability to concentrate the urine and many calcium phosphate casts were found. With skeletal mobilization the clinical picture began to improve rapidly, and at discharge the kidney function tests were normal. The interpretation of the sequence of events in this case by the authors was that more calcium was presented to the kidneys than could be handled, and hypercalcemia resulted; the hypercalcemia injured the renal tubules. When, by skeletal mobilization, the outflow of lime salts from the bones was allayed, the situation soon righted itself and no permanent residual kidney injury was found to have resulted.

That hypercalcemia can of itself cause renal injury seems altogether likely. Other conditions commonly associated with hypercalcemia are hy-

[1] Orr, W. J.: Personal communication—to be published.
[2] Wilkins, L.: Personal communication.
[3] Albright, F., Burnett, C. H., Cope, O., and Parson, W.: Acute atrophy of bone (osteoporosis) simulating hyperparathyroidism, Jr. Clin. Endocrinology, 1941, i, 711.

perparathyroidism and over-vigorous therapy with products of irradiated ergosterol, and in both of these renal damage is very common. Hypercalcemia occurs sometimes, of course, in extensive destructive bone diseases such as carcinomatosis and multiple myeloma.

We wish to point out and emphasize here that, with bone atrophy of disuse, *hypercalcemia and renal damage can occur.* That there must be factors operating other than atrophy of disuse alone seems obvious, for otherwise everyone with fractures warranting extensive skeletal immobilization would develop uremia. What these other factors may be remains unknown for the present. We may postulate, however, that certain factors would tend to make more likely the development of the syndrome, for example:

(1) A rapidly growing bone which, in a child, is supposed also to atrophy more rapidly. Hence we would expect to find the syndrome more common among children than among adults.

(2) Mobilization of lime salts from the strong dense bones of a day laborer would present the kidney with more work than if the immobilized patient were a sedentary worker or one who, for some other reason, already had rarefied bones.

(3) Anything which would tend to raise the serum calcium, such as the administration of large amounts of calcium, especially if vitamin D were given in addition. There is some reason to believe that vitamin D may be a much more vigorous agent in elevating the serum calcium when the patient is in bed than when he is up and about. Butler [4] has made an interesting observation in patients with resistant rickets. These patients require 300,000 to 1,000,000 I.U. calciferol per day in the ambulatory state to remain free of evidences of rickets and to keep the serum calcium and phosphorus levels normal. When such a patient is brought into the hospital and immobilized, this same dose of calciferol proves far too high and hypercalcemia rapidly ensues. The administration of "high milk diets and vitamin D" is a very common practice on fracture services, and one wonders if the use of these measures had not best be much more closely supervised.

(4) The use of alkalis can, under certain circumstances, produce calcification of renal tubules. The production of an alkaline urine would also tend to make more likely the precipitation of calcium phosphate and hence the production of urinary lithiasis.

(5) Certain types of renal injury, such as would reduce the ability to excrete calcium, would tend to cause or increase the hypercalcemia. As a matter of fact, the renal tubular injury caused by the hypercalcemia may reduce the functional ability to excrete calcium, and thus a vicious circle would be set up. Much more knowledge in regard to exact localization of renal tubular function will have to be available before we can speculate further along these lines.

[4] BUTLER, A. M.: Personal communication—to be published.

(6) An inadequate output of water would tend to precipitate the lime salts in the urine by increasing their concentration. It would also tend to act in the direction of lessened excretion by the kidneys and hence would favor hypercalcemia. It would seem wise, therefore, to force fluids to the point of insuring an adequate output of urine in cases with much skeletal immobilization.

Although a considerable portion of the above discussion is based on indirect evidence, the observation that sufficient renal damage may occur in association with states of skeletal rarefaction as to produce severe renal damage is of the greatest importance. Further work of a fundamental nature on the subject seems definitely indicated. Certain hitherto unidentified toxic states may be found to be due to hypercalcemia, and the frequent occurrence of uremia in elderly patients with fractures may be due, in some instances, to such a mechanism.

J. E. H.

REVIEWS

Practical Bedside Diagnosis and Treatment. By HENRY JOACHIM, M.D., F.A.C.P. 828 pages; 26 × 16.5 cm. Charles C. Thomas, Springfield, Illinois. 1940. Price, $7.50.

In his preface to this volume, the author states that it is largely a presentation of his own experiences during 35 years of practice and teaching, emphasizing bedside diagnosis and treatment. This personal touch is noticeable throughout the book, as it is written informally, in an almost conversational style.

There is, however, nothing in the plan of presentation of the subject matter that could facilitate differential diagnosis. The grouping of diseases is identical with that used in most standard textbooks of medicine. Some important diseases are omitted or neglected. For example, Rocky Mountain spotted fever is given only two lines, whereas many less important infections are described in detail.

In some cases, the recommended treatment leaves something to be desired, notably the description of the serum therapy of pneumonia.

In general, "Practical Bedside Diagnosis and Treatment" is a sound enough textbook, but is probably not up to the standards of other texts readily available to the student and practitioner.

T. N. C.

The Premature Infant; Its Medical and Nursing Care. By JULIUS H. HESS, M.D., and EVELYN C. LUNDEEN, R. N. 309 pages; 21 × 14 cm. J. B. Lippincott Co., Philadelphia. 1941. Price, $3.50.

"The Premature Infant," a very excellent and authoritative work, is divided into 28 chapters. The first few chapters discuss the classification of prematures, their etiology, physiologic development, and growth. Approximately the next 150 pages are devoted to nursing routines, nursery requirements, feedings, transportation, etc. Clinical conditions, such as cyanosis, hemorrhage, respiratory diseases, anemia, syphilis, etc., are discussed in the last 10 chapters.

Emphasis is especially placed on nursing care and nursery requirements. This is done in a very unified and detailed manner. Home care for the premature is also explained. The clinical subjects are not discussed in great detail, but only as these conditions affect the premature.

W. M. S.

Diseases of the Thyroid Gland. By ARTHUR E. HERTZLER, M.D. 670 pages; 26 × 19 cm. Paul B. Hoeber, Inc., New York City. 1941. Price, $8.50.

Dr. Hertzler, best known to the American public as the author of "The Horse and Buggy Doctor," states that this book is "in no wise a treatise on diseases of the thyroid gland, but a record of his studies extending over a period of nearly fifty years." This statement explains the almost complete absence of discussion of the work of other investigators, and the scarcity of references to the medical literature, of which only six are given in the entire book. Of the six articles referred to, four are written by members of Dr. Hertzler's clinic. Several chapters are written by associates.

The author's personality and opinions dominate the material presented. A vivid method of writing, exemplified in Dr. Hertzler's autobiography, has been used in the present work. Occasionally the style serves to hold the reader's interest, but more often the anecdotes and pungent comments lead to confusion and interruption of one's train of thought.

It is unfortunate that practically no statistical analysis of Dr. Hertzler's great mass of material is presented, except in the chapter on hepatic insufficiency by C. R.

Schmidt. This is especially disappointing when one considers that the author devotes a great deal of space to his attempt to prove that total thyroidectomy in the adult is never followed by myxedema, and that myxedema associated with a palpable thyroid can be cured by the removal of the gland. Statistics might also reinforce the author's opinions on cardiotoxic goiter, as described in chapter seven.

Dr. Hertzler has drawn liberally on his great store of pathologic material. The book is profusely illustrated, chiefly by photographs of gross and microscopic sections of glands removed at operation. The chapter on thyroiditis, describing suppurative and nonsuppurative thyroiditis, Hashimoto's and Riedell's strumas, is one of the best.

Except for a slip on page 515, the Publisher bears out his reputation as a maker of beautiful medical books.

T. N. C.

The Minds and Nerves of Soldiers. By EDWARD L. HANES, M.D. 221 pages; 23.5 × 16 cm. The Logan Press, Pasadena, California. 1941. Price, $3.00.

This is essentially an autobiography in which the author sets forth his experiences while serving as a neuropsychiatrist with the A. E. F. during the First World War. The material is not very well integrated or organized, and the attempt to coördinate past experiences with the vital needs of the present is weak. One-third of the book consists of case records covering a wide range of neuropsychiatric disabilities in which the author presents his clinical experiences and this is mostly descriptive in fashion. The remainder is devoted to the author's personal experiences, his impressions and his philosophy as it is related to military psychiatry.

Possibly the book is of some value to the beginner in this specialty but it has little to offer the trained neuropsychiatrist aside from its historical interest. From it, one is impressed by a need in the armed forces of a sufficient number of psychiatrists not only to detect and eliminate potential mental disabilities but also to provide adequate care and treatment of essentially a personal, highly individualized nature.

H. W. N.

Emotions and Bodily Changes: A Survey of Literature on Psychosomatic Interrelationships, 1910–1933. Second Edition. By H. FLANDERS DUNBAR, M.D., Med.Sc.D., Ph.D. 601 pages; 24 × 16 cm. Columbia University Press, New York City. 1938. Price, $5.00.

Medical men have always recognized and been curious about the fact that mental states do influence bodily processes and are influenced by them in turn. This curiosity regarding the influence of "mind over body" has only recently taken the form of serious scientific research. The phrase "psychosomatic medicine" has been coined to express this new interest. Psychiatrists have long taught us that it is futile to think of diseases as being caused either by organic or psychogenic factors. The organism as a whole (mind and body) is involved in every pathologic process, whether attention is focused on etiology, course or treatment.

Dr. Dunbar has been a pioneer in psychosomatic medicine, in studying scientifically this baffling problem. Her book, Emotions and Bodily Changes, must be referred to by anyone who wants to study or contribute to this field. Although this field is comparatively new, much ground work was done during the period 1910 to 1933. Incidentally, the present edition surveys much of the literature which appeared since the first edition (1935).

This book is primarily intended for reference, and has excellent subject and author indices. But in spite of the fact that 2358 articles are quoted from or referred to, it is logically arranged and presented in very readable form. Especially valuable to read are the first chapters, dealing with the problems studied and the methods for studying them, and the final chapter on therapeutic considerations. Certainly no medical library is complete if it does not have this book, in its latest edition, for reference.

H. W. N.

COLLEGE NEWS NOTES

Gifts to the College Library

We gratefully acknowledge receipt of the following gifts donated to the College Library of Publications by Members:

Books

Dr. Jerome E. Andes, F.A.C.P., Tucson, Ariz.—"Synopsis of Applied Pathological Chemistry";
Dr. Hugh R. Butt, F.A.C.P. and Dr. Albert M. Snell, F.A.C.P., Rochester, Minn.—"Vitamin K";
Dr. Reginald Fitz, F.A.C.P., Boston, Mass.—"The Surprising Career of Peter La Terrière, Bachelor in Medicine";
Dr. John A. Kolmer, F.A.C.P., Bala-Cynwyd, Pa.—"Approved Laboratory Technic" and "Clinical Immunology, Biotherapy and Chemotherapy";
Dr. James Ralph Scott, F.A.C.P., New York, N. Y.—"Diabetes";
Joseph F. Siler, F.A.C.P., Col., (MC), U. S. Army, Retired—"Immunization to Typhoid Fever";
Dr. Gerald B. Webb, F.A.C.P., Colorado Springs, Colo.—"Tuberculosis";
Dr. John B. Youmans, F.A.C.P., Nashville, Tenn.—"Essentials of the Diagnostic Examination."

Reprints

Dr. Marcus Backer, F.A.C.P., Bridgeport, Conn.—1 reprint;
Dr. N. Judson Bender (Associate), Shreveport, La.—1 reprint;
Dr. J. Edward Berk (Associate), Philadelphia, Pa.—4 reprints;
Dr. Nathan Blumberg, F.A.C.P., Philadelphia, Pa.—1 reprint;
Dr. Grafton Tyler Brown, F.A.C.P., Washington, D. C.—1 reprint;
Dr. Anthony V. Cadden, F.A.C.P., Wauwatosa, Wis.—2 reprints;
Dr. Verne S. Caviness, F.A.C.P., Raleigh, N. C.—2 reprints;
Dr. Fred M. Drennan, F.A.C.P., Chicago, Ill.—1 reprint;
Dr. Reginald C. Edson (Associate), Hopemont, W. Va.—1 reprint;
Dr. William Freeman, F.A.C.P., Worcester, Mass.—1 reprint;
Dr. Charles F. Gormly, F.A.C.P., Providence, R. I.—3 reprints;
Dr. Elmer Haynes (Associate), Madison, Wis.—2 reprints;
Dr. Lyman H. Hoyt, F.A.C.P., Boston, Mass.—2 reprints;
Dr. Edward Kupka, F.A.C.P., Los Angeles, Calif.—2 reprints;
Oza J. LaBarge, F.A.C.P., Lieut., (MRC), U. S. Army—1 reprint;
Dr. Michael Lake, F.A.C.P., New York, N. Y.—1 reprint;
Dr. David O. N. Lindberg, F.A.C.P., San Diego, Calif.—1 reprint;
Dr. Philip H. Livingston, F.A.C.P., Chattanooga, Tenn.—1 reprint;
Dr. David Salkin, F.A.C.P., Hopemont, W. Va.—2 reprints;
Dr. David J. Sandweiss, F.A.C.P., Detroit, Mich.—5 reprints;
Dr. Philipp J. R. Schmahl, F.A.C.P., New York, N. Y.—1 reprint;
Dr. James Ralph Scott, F.A.C.P., New York, N. Y.—3 reprints;
Dr. Christopher C. Shaw, F.A.C.P., Warrington, Fla.—1 reprint;
Dr. Albert Soiland, F.A.C.P., Los Angeles, Calif.—2 reprints;
Dr. Frederick G. Speidel, F.A.C.P., Louisville, Ky.—1 reprint.

Regional Meeting of Illinois Members

The first Regional Meeting of Fellows and Associates in the northern district of Illinois was held at Chicago, December 6, 1941, but the meeting was expanded to include the entire state. Dr. LeRoy H. Sloan, Chicago, Governor for Northern Illinois, and Dr. Cecil M. Jack, Decatur, Governor for Southern Illinois, conducted the meeting in collaboration, and College members from near-by points in the adjoining states of Wisconsin, Indiana, and Michigan were also invited.

Dr. George H. Coleman, Chicago, was Chairman of the Committee on Arrangements, and Dr. Willard O. Thompson, Chicago, was Chairman of the Program Committee. The program, starting at 9:00 a.m., was as follows:

Morning Session

Governor Cecil M. Jack, *Presiding*

9:00 "Treatment of Experimental Renal Hypertension with Renin." G. E. Wakerlin and C. A. Johnson, Chicago.

9:10 "Carcinoma of the Pancreas: A Clinical and Pathological Study of 75 Cases." Aaron Arkin and S. W. Weisberg, Chicago.

9:20 "Thiamin in Perspiration." Leo Hardt and Eugene U. Still, Ph.D., Chicago.

9:30 "Improved Methods of Diagnosis of Protozoan Infections of the Intestine." Alva A. Knight, Chicago.

9:40 "Diagnostic Problems in Coronary Thrombosis." E. W. Cannady, East St. Louis.

Intermission (10 minutes)

10:00 "Effects of Various Mixtures of Insulin and Protamine Zinc Insulin." Arthur R. Colwell, Evanston.

10:10 "Chronic Combined Acetanilid and Amidopyridine Poisoning: A Case Report." V. Thomas Austin, Urbana.

10:20 "Pneumonia in an Army Station Hospital in 1941." Emmet H. Pearson, Fort Sheridan.

10:45 to 12:00 Clinico-pathologic Conference. Conducted by James P. Simonds, Professor of Pathology, Northwestern University Medical School. *Clinicians:* Ralph C. Brown, James G. Carr, Joseph A. Capps.

Luncheon

12:00–1:00 p.m. Luncheon in the Dining Room of New Wesley Memorial Hospital. Written questions on the morning program were submitted and answered at a round table discussion during Luncheon with Governor LeRoy H. Sloan, presiding.

1:00–2:00 p.m. Inspection of Hospital. Drs. Raymond McNealy and Gilbert Marquardt.

Afternoon Session

2:00–3:30 Medical Progress in Review. Willard O. Thompson, presiding. (Each presentation limited to 5 minutes.)

"Diabetes."	Robert W. Keeton.
"Diseases of the Liver."	Sidney A. Portis.
"Chemotherapy."	Paul Rhoads.
"Pneumonia."	Italo F. Volini.
"Contagious Diseases."	Archibald A. Hoyne.
"Surgical Shock."	Warren Cole.
"Physiology."	Andrew C. Ivy.
"Hypertension."	M. Herbert Barker.

"Vitamins."	Clifford Barborka.
"Endocrinology."	Willard O. Thompson.
"Arthritis."	Ernest E. Irons.
"Cardiology."	Gilbert Marquardt.
"Pancreatic Hormones."	Lester R. Dragstedt.
"Peptic Ulcer."	Walter L. Palmer.

Vice-President Samuel E. Munson, *Presiding*

3:30 "Irradiation of the Pituitary and Adrenals for Essential Hypertension." James H. Hutton, Chicago.

3:40 "Mechanism of Death from Mercurial Diuretics." Howard Lindberg, Maurice Thomas and M. Herbert Barker, Chicago.

3:50 "Rôle of Emotions in Medicine." F. J. Braceland, Chicago.

4:00 "Rôle of Stimulants in the Treatment of Barbiturate Poisoning." Richard Kohn Richards, North Chicago.

4:10 "Present Status of Stilbestrol." S. G. Taylor, III and W. O. Thompson, Chicago.

4:20 "Specific Precipitin Antisera for Tissue Proteins." William H. Welker, Chicago.

4:30 "Medical Preparedness." Major Harold Lueth, Chicago.

There were a number of subjects for general discussion which, due to lack of time, were read by title.

The evening program was held at the Knickerbocker Hotel, consisting of a social hour followed by dinner, after which Dr. Edward L. Bortz, F.A.C.P., Philadelphia, presented an address on "Medical Progress and the American College of Physicians." Short talks were made by distinguished guests, and Dr. George Coleman presided as Toastmaster.

Approximately 150 members were in attendance. This meeting was the first medical scientific meeting to be held in the New Wesley Memorial Hospital on the Campus of Northwestern University.

Regional Meeting of Maryland Members

The fall meeting of the Maryland Chapter of the American College of Physicians was held at a dinner at the Belvedere Hotel on Thursday December 18, 1941. There were 67 present including guests, Dr. Thomas Rivers, Director of the Rockefeller Institute, Mr. E. R. Loveland, Executive Secretary of the College, and the resident physicians of a number of the Baltimore hospitals. Dr. John King, President of the Maryland Chapter, presided. Dr. King introduced Mr. Loveland who brought greetings from Dr. Roger Lee, President of the College. Mr. Loveland spoke of the growth of the College, the work of the College in Defense, and concluded with the advice that we should "protect our American Institutions and our College."

Dr. King next introduced Dr. Thomas Rivers who gave a very stimulating talk on the physical, chemical and biological characteristics of vaccine virus.—Lewis P. Gundry, M.D., F.A.C.P., *Secretary*.

On December 10, 1941, Dr. Rufus S. Reeves, F.A.C.P., Philadelphia, Pa., spoke on "The Rôle of the Physician in Local Disasters" at a meeting on National Defense of the Philadelphia County Medical Society.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., presented a paper on "The Nutrition Needs of Our Community" as part of The Forum at The Nutrition Institute of Philadelphia, November 8, 1941.

Dr. Kelly also presented a paper on "Nutrition as It Applies to the General Diseases" and a film in natural color, "The Modern Science of Nutrition and Nutritional Deficiency Disease," before the Cambria County Medical Society at Johnstown, Pa., November 13, 1941.

John W. Shuman, Sr., F.A.C.P., Lt. Col., (MRC), U. S. Army, has been elected an honorary member of the Hollywood Academy of Medicine.

On July 21, 1941, George C. Turnbull (Associate), Captain (MRC), U. S. Army, was appointed Chief of the Medical Service at the Station Hospital, Fort Bliss, Tex.

Dr. James H. Hutton, F.A.C.P., and Dr. Robert S. Berghoff, F.A.C.P., both of Chicago, Ill., have been appointed members of the Board of Advisers in the Department of Public Health for the State of Illinois, by Governor Dwight H. Green.

Dr. Bernard E. McGovern, F.A.C.P., San Fernando, Calif., has been appointed Medical Director of Hillcrest Sanatorium, La Crescenta, Calif. Dr. McGovern has also become a member of the Tuberculosis Division of the Los Angeles City Health Department.

Dr. John M. Nicklas, F.A.C.P., Trudeau, N. Y., has recently been appointed a member of the Committee on Sanatorium Standards of the American Trudeau Society. Dr. Harold G. Trimble, F.A.C.P., Oakland, Calif., is President and Dr. Henry C. Sweany, F.A.C.P., Chicago, Ill., is President-Elect of this Society.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., addressed the Fall Clinical Conference of The Medical Society of New Jersey on December 3, 1941, at Elizabeth, N. J., on "Ulcer and Cancer of the Stomach in the Middle Ages."

The Alpha Nu Chapter of Phi Rho Sigma, located at the University of Texas Medical School, had inauguration of the Phi Rho Sigma Lectureship for the purpose of bringing before the students of this School eminent physicians. This lectureship has been established in honor of the deceased alumni of the chapter, many of whom have been prominent members of the Faculty of the University of Texas Medical School. The first lectures were given December 1, 1941 by Dr. R. E. Dyer on "Typhus Fever" and by Dr. R. L. Cecil, F.A.C.P., on "Rheumatoid Arthritis."

The Omaha Mid-West Clinical Society held its 9th Annual Assembly in Omaha, Nebr., October 27–31, 1941. Among the guest speakers at this meeting were:

Dr. W. Osler Abbott, F.A.C.P., Philadelphia, Pa.—"Nonsurgical Treatment of Obstruction of the Bowel," "The Action of Drugs on the Alimentary Tract" and "Functional Disorders of Digestion (Clinic)";

Dr. Byrl R. Kirklin, F.A.C.P., Rochester, Minn.—"The Early Manifestations of Gastrointestinal Cancer" and "Evaluation of Roentgenologic Methods in the Diagnosis of Diseases of the Gall-Bladder and Duodenum";

Dr. Albert M. Snell, F.A.C.P., Rochester, Minn.—"Recent Advances in Vitamin Therapy," "Supposedly Rare Conditions Producing Abdominal Pain" and "Diseases of the Liver and Bile Passages (Clinic)";

Dr. S. Bernard Wortis, F.A.C.P., New York, N. Y.—"Injury to the Brain and Spinal Cord," "Brain Metabolism and Neuropsychiatric Disorders" and "Brain Tumors (Clinic)."

The College members in Omaha who participated in this program were:

Dr. A. David Cloyd, F.A.C.P.—"The Mechanism, Recognition and Management of Congestive Heart Failure";

Dr. F. Lowell Dunn, F.A.C.P.—"The Visualization of Normal and Pathologic Chest Sounds by the Use of the Cathode Ray Tube";

Dr. Esley J. Kirk, F.A.C.P.—"Clinical Interpretation of the Various Laboratory Procedures of Hypertension and Nephritis";

Dr. George P. Pratt, F.A.C.P.—"The Incidence, Differential Diagnosis and Treatment of Bacillary Dysentery";

Dr. Chester Q. Thompson, F.A.C.P.—"Transfusions of Blood and Plasma";

Dr. Raymond L. Traynor, F.A.C.P.—"Clinical Manifestations of Vitamin B Deficiency";

Dr. Albert F. Tyler, F.A.C.P.—"Newer Radiographic Methods in Gastrointestinal Diagnosis";

Dr. Harrison A. Wigton, F.A.C.P.—"Hysteria and Personality";

Dr. J. Harry Murphy (Associate)—"The Early Recognition and Immediate Treatment of Cerebral Hemorrhage in the Newborn";

Dr. John C. Sharpe (Associate)—"Rheumatic Heart Disease."

Among the scientific exhibits the exhibit of Dr. F. Lowell Dunn, F.A.C.P. won the Premier Award for "Originality and excellence of individual investigation," and the exhibit of Dr. J. Harry Murphy, Assoc., won an honorable mention for "Excellence of presentation."

At a meeting of the Board of Directors of the Mississippi Valley Medical Society, November 23, 1941, Dr. Dan G. Stine, F.A.C.P., Columbia, Mo., was named President for 1942. Dr. F. Garm Norbury, F.A.C.P., Jacksonville, Ill., was named Second Vice-President and Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., was reëlected Secretary-Treasurer.

Dr. Nathan S. Davis, III, F.A.C.P., Chicago, Ill., and Dr. John H. Peck, F.A.C.P., Oakdale, Iowa, were elected to membership on the Board of Directors.

Dr. S. A. Slater was reëlected president of the Minnesota Public Health Association for the fifth consecutive term at the annual meeting of the organization in St. Paul recently.

Dr. Robert T. Terry (Associate), of the Letterman General Hospital, San Francisco, Calif., is incorrectly listed in the 1941 Directory of the American College of Physicians as being in the Medical Corps of the U. S. Army, whereas, he is a member of the Medical Reserve Corps of the Army, on active duty. Before entering active service he was in practice at Denver, Colo.

Dr. Joseph S. D'Antoni (Associate), New Orleans, La., was chosen Vice President of the American Society of Tropical Medicine at its meeting November 10–13, 1941, in St. Louis, Mo.

At the recent meeting of the American Clinical and Climatological Association, Dr. C. Sidney Burwell, F.A.C.P., Boston, Mass., was named President, and Dr. Maurice C. Pincoffs, F.A.C.P., Baltimore, Md., and Dr. Francis M. Rackemann, F.A.C.P., Boston, Mass., Vice-Presidents.

Dr. Willard C. Rappleye, F.A.C.P., Commissioner of Hospitals of the City of New York and Dean and Professor of Medical Economics at Columbia University College of Physicians and Surgeons, has been elected President of the Josiah Macy Jr. Foundation. This Foundation was organized to further medical education.

Dr. Joseph H. Barach, Pittsburgh, Pa., addressed the Lackawanna County Medical Society on November 25, 1941. His topic was "Pneumonia." On December 2, 1941, he spoke before the Westmoreland County Medical Society on "Diabetes and Its Complications."

New Elections to College Membership

At a meeting of the Board of Regents December 14, 1941, at the headquarters building, Philadelphia, the following candidates were regularly elected to the class indicated:

Elections to Fellowship

December 14, 1941

Fellowship Candidates	*Sponsors*
Arkansas	
John Herman Baird, North Little Rock	William B. Grayson, John R. Dibrell, Oliver C. Melson
California	
Horace Bicknell Cates, Los Angeles	E. Richmond Ware, Ernest C. Fishbaugh, Roy E. Thomas
Colorado	
Charles Douglas Deeds, Denver	Constantine F. Kemper, James R. Arneill, James J. Waring
Abe Ravin, Denver	John G. Ryan, Rudolph W. Arndt, James J. Waring
Alfred Martin Wolfe, Denver	Thomas D. Cunningham, James R. Arneill, James J. Waring
John I. Zarit, Denver	Mathew A. Spangelberger, Harry Gauss, James J. Waring
Connecticut	
Charles Tiffany Bingham, Hartford	G. Gardiner Russell, John A. Wentworth, Charles H. Turkington
Peter J. Steincrohn, Hartford	Orin R. Witter, Otto G. Wiedman, Charles H. Turkington
Charles Russman, Middletown	Roy L. Leak, F. Erwin Tracy, Charles H. Turkington
Robert Hough Jordan, New Haven	Theodore S. Evans, Charles J. Bartlett, Charles H. Turkington
William Thomas Salter, New Haven	George R. Minot, J. H. Means, William B. Breed
Delaware	
John William Pendleton Love, New Castle	George H. Gehrmann, Bartholomew M. Allen, Lewis B. Flinn
District of Columbia	
Worth Bagley Daniels, Washington	Matthew W. Perry, James P. Leake, Wallace M. Yater
Leon Stuart Gordon, Washington	Tomás Cajigas, William Gerry Morgan, Wallace M. Yater
Medical Corps, U. S. Army	
Clifford Gordon Blitch, Washington, D. C.	James C. Magee
Medical Corps, U. S. Navy	
George Brackett Dowling, San Francisco, Calif.	Roy J. Leutsker, Joel J. White, Ross T. McIntire
Edward Patrick McLarney, Jacksonville, Fla.	Ross T. McIntire

Fellowship Candidates	*Sponsors*
U. S. Public Health Service	
Guy Henry Faget, Carville, La.	Thomas Parran
Alvin Randolph Sweeney, Ellis Island, N. Y.	Thomas Parran
Florida	
Theodore Ferdinand Hahn, Jr., DeLand	Louie M. Limbaugh, J. Webster Merritt, T. Z. Cason
Karl Boyles Hanson, Jacksonville	Louie M. Limbaugh, J. Webster Merritt, T. Z. Cason
Lincoln Sydnor Laffitte, Jacksonville	Louie M. Limbaugh, James L. Borland, T. Z. Cason
Franz Hahr Stewart, Miami	Paul B. Welch, Mathew J. Flipse, T. Z. Cason
Paul Kastli Jenkins, Miami Beach	Charles F. Roche, Robert M. Harris, T. Z. Cason
Georgia	
Bernard Preston Wolff, Atlanta	T. Sterling Claiborne, Roy S. Leadingham, Glenville Giddings
Richard Hugh Wood, Atlanta	H. Cliff Sauls, Carter Smith, Glenville Giddings
Hervey Milton Cleckley, Augusta	Virgil P. Sydenstricker, Joseph D. Gray, Glenville Giddings
George Leonard Walker, Griffin	Trimble Johnson, Hal M. Davison, Glenville Giddings
Illinois	
Jay Bailey Carter, Chicago	Willard O. Thompson, Lee C. Gatewood, LeRoy H. Sloan
Israel Davidsohn, Chicago	Josiah J. Moore, Malcolm T. MacEachern, LeRoy H. Sloan
Frank B. Queen, Chicago	Rudolph W. Arndt, John G. Ryan, James J. Waring
Willard Leo Wood, Chicago	Willard O. Thompson, Lee C. Gatewood, LeRoy H. Sloan
Paul Spottswood Rhoads, Evanston	James G. Carr, Samuel J. Lang, LeRoy H. Sloan
Eugene Fagan Traut, Oak Park	Willard O. Thompson, Lee C. Gatewood, LeRoy H. Sloan
Indiana	
Ralph Ulrich Leser, Indianapolis	Edgar F. Kiser, Rollin H. Moser, Robert M. Moore
Iowa	
James Leon Dubrow, Des Moines	Walter L. Bierring, John H. Peck, Fred M. Smith
Kansas	
John Lewis Kleinheksel, Wichita	Henry N. Tihen, Fred J. McEwen, Harold H. Jones
Earl Lee Mills, Wichita	Thomas T. Holt, Henry N. Tihen, Harold H. Jones
Kentucky	
Luther Bach, Newport	William E. Gardner, Arthur C. McCarty, C. W. Dowden
Louisiana	
Donovan Clarence Browne, New Orleans	Randolph Lyons, John H. Musser, Joseph E. Knighton
George Edward Burch, New Orleans	John H. Musser, Grace A. Goldsmith, Joseph E. Knighton
Elliston Farrell, New Orleans	Tasker Howard, J. Hamilton Crawford, C. F. Tenney, Joseph E. Knighton

Fellowship Candidates	*Sponsors*
William Howard Gillentine, New Orleans	John H. Musser, Philip H. Jones, Jr., Joseph E. Knighton
Herbert John Schattenberg, New Orleans	John H. Musser, Philip H. Jones, Jr., Joseph E. Knighton
William Anthony Sodeman, New Orleans	John H. Musser, Grace A. Goldsmith, Joseph E. Knighton
MARYLAND	
Robert William Garis, Baltimore	Sydney R. Miller, Edwin B. Jarrett, Louis Krause
Henry Mathies Hensen, Baltimore	Wetherbee Fort, Sydney R. Miller, Louis Krause
Charles Franklin Mohr, Baltimore	Wetherbee Fort, Edwin B. Jarrett, Louis Krause
Hugh Grigsby Whitehead, Baltimore	Louis Hamman, Sydney R. Miller, Louis Krause
MASSACHUSETTS	
George Parkman Denny, Boston	Albert A. Hornor, James H. Townsend, William B. Breed
Burton Everett Hamilton, Boston	Elliott P. Joslin, Howard F. Root, William B. Breed
William Timothy O'Halloran, Boston	John A. Foley, James M. Faulkner, William B. Breed
Richard Pratt Stetson, Boston	George R. Minot, J. H. Means, William B. Breed
Lowrey Frederick Davenport, Brookline	Donald S. King, Dwight L. Siscoe, William B. Breed
MICHIGAN	
Sidney Adler, Detroit	Hugo A. Freund, Edward D. Spalding, Henry R. Carstens
Emil M. Shebesta, Detroit	Rollin H. Stevens, Charles E. Lemmon, Henry R. Carstens
Lloyd Bennett Young, Detroit	George B. Hoops, Rollin H. Stevens, Henry R. Carstens
MINNESOTA	
Arthur Carl Kerkhof, Minneapolis	S. Marx White, Harry E. Ungerleider, Edgar V. Allen
Alexander Robinson MacLean, Rochester	Albert M. Snell, Henry W. Woltman, Edgar V. Allen
Edward Frank Rosenberg, Rochester	Philip S. Hench, Albert M. Snell, Edgar V. Allen
Jan Henrik Tillisch, Rochester	Harold C. Habein, Nelson W. Barker, Edgar V. Allen
MISSISSIPPI	
Wesley Wayne Lake, Pass Christian	Ben R. Heninger, Randolph Lyons, John G. Archer
MISSOURI	
William Byrne Brown, Columbia	Dan G. Stine, Howard A. Rusk, A. Comingo Griffith
Carl Vernon Moore, Jr., St. Louis	Harry L. Alexander, Louis H. Behrens, David P. Barr, A. Comingo Griffith
Francis Bacon Camp, Springfield	G. Bruce Lemmon, Elmer E. Glenn, A. Comingo Griffith
MONTANA	
Alf Cornelius Johnson, Great Falls	Harold W. Gregg, Malcolm D. Winter, Ernest D. Hitchcock
Thomas Franklin Walker, Great Falls	Richard B. Durnin, Harold W. Gregg, Ernest D. Hitchcock
NEW HAMPSHIRE	
Harold David Levine, Bristol	Henry A. Christian, Colin C. Stewart, Robert B. Kerr

Fellowship Candidates	*Sponsors*
Nathan Townley Milliken, Hanover	Harry T. French, Colin C. Stewart, Robert B. Kerr
NEW JERSEY	
Samuel Cohen, Jersey City	Thomas J. White, J. Burns Amberson, Jr., George H. Lathrope
Samuel Irving Kooperstein, Jersey City	Abraham E. Jaffin, Berthold S. Pollak, George H. Lathrope
Charles Andrew Landshof, Jersey City	Thomas J. White, Harry J. Perlberg, George H. Lathrope
Elizabeth Brakeley, Montclair	Harvey M. Ewing, Irving S. Wright, George H. Lathrope
William George Bernhard, Newark	John W. Gray, Edward C. Klein, Jr., George H. Lathrope
NEW MEXICO	
Walter Ignatius Werner, Albuquerque	Ralph W. Mendelson, John R. Van Atta, LeRoy S. Peters
NEW YORK	
Saverio Charles Franco, Brooklyn	Albert F. R. Andresen, Frederick Schroeder, C. F. Tenney
Alfred Peter Ingegno, Brooklyn	Tasker Howard, Albert F. R. Andresen, C. F. Tenney
Emanuel Schwartz, Brooklyn	Albert F. R. Andresen, Tasker Howard, C. F. Tenney
Ramsdell Gurney, Buffalo	Abraham H. Aaron, Stockton Kimball, Nelson G. Russell
Lawrence Edgar Hummel, Buffalo	Abraham H. Aaron, Clayton W. Greene, Nelson G. Russell
Francis Emmett Kenny, Buffalo	Walter H. Krombein, Harvey C. Schneider, Nelson G. Russell
Dwight Turney Bonham, Hempstead	Willard J. Davies, Louis H. Bauer, C. F. Tenney
Benjamin Roy Allison, Hewiett	Henry T. Chickering, Russell L. Cecil, C. F. Tenney
Jacob Ernest Nadler, Jackson Heights	Arthur C. DeGraff, Norman Jolliffe, C. F. Tenney
Harold Albert Butman, Manhasset	Louis H. Bauer, Willard J. Davies, C. F. Tenney
Alexander John Chilko, New Rochelle	Arthur F. Heyl, George W. Cramp, C. F. Tenney
Arthur Joseph Antenucci, New York	Howard F. Shattuck, Asa L. Lincoln, C. F. Tenney
Harold Brandaleone, New York	Elaine P. Ralli, Norman Jolliffe, C. F. Tenney
Frank Miller Falconer, New York	Howard F. Shattuck, Peter Irving, C. F. Tenney
John Alexander Clinton Gray, New York	Howard F. Shattuck, Robert A. Cooke, C. F. Tenney
William Hall Lewis, Jr., New York	Asa L. Lincoln, Cornelius P. Rhoads, C. F. Tenney
Putnam Crocker Lloyd, New York	William W. Herrick, Randolph West, Walter W. Palmer, C. F. Tenney
Walter Lindsay Niles, New York	Robert A. Cooke, George Morris Piersol, C. F. Tenney
Leon Arthur Salmon, New York	Charles A. McKendree, A. Wilbur Duryee, C. F. Tenney
Christopher Parnall, Jr., Rochester	David B. Jewett, Charles B. F. Gibbs, Nelson G. Russell
Daniel Milton Brumfiel, Saranac Lake	John N. Hayes, William S. McCann, Nelson G. Russell
Walter Carl Hausheer, Staten Island	Arthur C. DeGraff, George G. Ornstein, James Alex. Miller, C. F. Tenney
John Michael Nicklas, Trudeau	John K. Deegan, J. Burns Amberson, Jr., C. F. Tenney
Thomas Douglas Kendrick, Utica	Andrew Sloan, William A. Groat, Nelson G. Russell
Charles Wesley Martin, Woodmere	Louis H. Bauer, Louis A. Van Kleeck, C. F. Tenney

Fellowship Candidates	*Sponsors*
North Carolina	
Charles Darwin Thomas, Sanatorium	Paul P. McCain, William T. Rainey, C. H. Cocke
North Dakota	
Paul Jean Breslich, Minot	Paul H. Rowe, Robert B. Radl, Julius O. Arnson
Ohio	
Arthur Dale Nichol, Cleveland	Charles T. Way, Harry D. Piercy, A. B. Brower
Ruth Alice Koons, Columbus	R. W. Kissane, Charles A. Doan, A. B. Brower
Lewis Kerr Reed, Youngstown	William H. Bunn, Colin R. Clark, Roy W. Scott, A. B. Brower
Oklahoma	
Richard Michael Burke, Clinton	Frank L. Jennings, Ben H. Cooley, Lea A. Riely
Minard Friedberg Jacobs, Oklahoma City	Wann Langston, John E. Heatley, Lea A. Riely
Samuel Goodman, Tulsa	Russell C. Pigford, Homer A. Ruprecht, Lea A. Riely
Oregon	
Max William Hemingway, Bend	Ernest L. Boylen, John H. Fitzgibbon, Homer P. Rush
Irvin Reginald Fox, Eugene	Fredrick A. Willius, Albert H. Ross, Homer P. Rush
Guy Robert McCutchan, Portland	William E. Ash, Aldis A. Johnson, Homer P. Rush
Pennsylvania	
Alfred Winfield Dubbs, Allentown	Thomas Klein, Willard D. Kline, Edward L. Bortz
Abraham Max Balter, Aspinwall	Kelso A. Carroll, Charles M. Griffith, R. R. Snowden
William Freas Confair, Benton	William Devitt, Harold L. Tonkin, Edward L. Bortz
Claude Wilber Ashley, Bloomsburg	Carl E. Ervin, Arthur E. Davis, Edward L. Bortz
Robert Deming Donaldson, Kane	George J. Kastlin, James M. Strang, R. R. Snowden
William Osler Abbott, Philadelphia	T. Grier Miller, Charles C. Wolferth, Edward L. Bortz
Theodore Lyle Hazlett, Pittsburgh	C. Howard Marcy, Howard G. Schleiter, R. R. Snowden
Rhode Island	
Cecil Calvert Dustin, Providence	Henry L. C. Weyler, Isaac Gerber, Alex. M. Burgess
Robert Gordon Murphy, Providence	Charles F. Gormly, Herman A. Lawson, Alex. M. Burgess
Tennessee	
Carl Adam Hartung, Chattanooga	James L. Bibb, Franklin B. Bogart, William C. Chaney
Wallace Lamar Poole, Johnson City	Frank L. Roberts, Horton R. Casparis, J. O. Manier
Texas	
Max Erwin Suehs, Beaumont	Lee T. Pruit, Victor M. Longmire, M. D. Levy
Cecil Overton Patterson, Dallas	David W. Carter, Jr., Milford O. Rouse, M. D. Levy
Loyd Webster Sheckles, Jr., Galveston	George R. Herrmann, Raymond L. Gregory, M. D. Levy
Edward Albert Wilkerson, Houston	Frederick R. Lummis, LeRoy B. Duggan, M. D. Levy

Fellowship Candidates	*Sponsors*
VIRGINIA	
Walter Lewis Nalls, Richmond	Dean B. Cole, R. Finley Gayle, Jr., Walter B. Martin
John Braxton McKee, Winchester	Dean B. Cole, R. Finley Gayle, Jr., Walter B. Martin
WASHINGTON	
Donald Ainslie Palmer, Spokane	George H. Anderson, Edwin G. Bannick, Charles E. Watts
Max Singer Wright, Spokane	George H. Anderson, Carl S. Leede, Charles E. Watts
REPUBLIC OF PANAMA	
Amadeo Vicente-Mastellari, Panama	Henry C. Dooling, Tomás Guardia, William M. James
CHINA	
Frederick Gilman Scovel, Tsining	Chester N. Frazier, Henry S. Houghton, Henry M. Thomas, Jr.

"RESOLVED, that the following list of 5 be and herewith are elected to Fellowship in the American College of Physicians as of April 19, 1942":

CALIFORNIA	
Archie Marvin Roberts, Los Angeles	E. Richmond Ware, George H. Houck, Roy E. Thomas
Delbert H. McNamara, Santa Barbara	Harry E. Henderson, Hildahl I. Burtness, Roy E. Thomas
MEDICAL CORPS, U. S. ARMY	
Kenneth George Gould, Montgomery, Ala.	James C. Magee
U. S. PUBLIC HEALTH SERVICE	
Clifton Keck Himmelsbach, Lexington, Ky.	Thomas Parran
OHIO	
Louis Bonner Owens, Cincinnati	William L. Freyhof, John H. Skavlem, A. B. Brower

ELECTIONS TO ASSOCIATESHIP

December 14, 1941

Associateship Candidates	*Sponsors*
ARKANSAS	
Ely Driver Rowland, Hot Springs National Park	Samuel G. Shepherd, Euclid M. Smith, Oliver C. Melson
Gerald Blankfort, Little Rock	Paul C. Eschweiler, Euclid M. Smith, Oliver C. Melson
Fred William Harris, Little Rock	Paul C. Eschweiler, Euclid M. Smith, Oliver C. Melson
CALIFORNIA	
Jesse Headen Inman, Bakersfield	George H. Houck, Arthur Stanley Granger, Roy E. Thomas
Lawrence Arthur Williams, Pasadena	B. O. Raulston, Alvin G. Foord, Roy E. Thomas
Walter Beckh, San Francisco	Dwight L. Wilbur, Arthur L. Bloomfield, Ernest H. Falconer
Richard Dufficy Friedlander, San Francisco	Dudley W. Bennett, Stacy R. Mettier, Ernest H. Falconer
John Orren Vaughn, Santa Monica	Roland Cummings, Raymond Sands, Roy E. Thomas

Associateship Candidates	*Sponsors*
COLORADO	
David Wilson McCarty, Jr., Longmont	Clough Turrill Burnett, James R. Arneill, James J. Waring
CONNECTICUT	
Samuel Nesbitt, New Haven	Albert M. Snell, Samuel F. Haines, Edgar V. Allen, Charles H. Turkington
DISTRICT OF COLUMBIA	
George James Stuart, Washington	Matthew W. Perry, Walter A. Bloedorn, Wallace M. Yater
MEDICAL CORPS, U. S. ARMY	
John Kemp Davis, Washington, D. C.	James C. Magee
William Bell Foster, Washington, D. C.	James C. Magee
Floyd Vern Kilgore, Fort Sill, Okla.	James C. Magee
Dwight Lawson, Hot Springs National Park, Ark.	James C. Magee
David Ernest Liston, Takoma Park, D. C.	James C. Magee
George Barnard Moore, Jr., Camp Claiborne, La.	William C. Pollock, George F. Aycock, James C. Magee
Ernest Holden Parsons, Atlanta, Ga.	James C. Magee
Arthur Eugene White, Hot Springs National Park, Ark.	James C. Magee
MEDICAL CORPS, U. S. NAVY	
Cecil Lenzora Andrews, San Diego, Calif.	Joel J. White, Roy J. Leutsker, Ross T. McIntire
Leon Delwin Carson, Washington, D. C.	John R. Poppen, E. Richison, Ross T. McIntire
Vincent Hernandez, Washington, D. C.	John Harper, E. Richison, Ross T. McIntire
Jerome Frost Smith, San Diego, Calif.	Joel J. White, Roy J. Leutsker, Ross T. McIntire
U. S. PUBLIC HEALTH SERVICE	
Gordon Arthur Abbott, Stapleton, Staten Island, N. Y.	Thomas Parran
Kenneth William Chapman, Lewisburg, Pa.	Thomas Parran
Thomas Royle Dawber, Boston, Mass.	Thomas Parran
Waldemar Claus Dreessen, Bethesda, Md.	Thomas Parran
Robert Harrold Flinn, Bethesda, Md.	Thomas Parran
Eugene Willard Green, Springfield, Mo.	Thomas Parran
William David King, San Francisco, Calif.	Thomas Parran
Harold Dwight Lyman, Springfield, Mo.	Thomas Parran
Albert Taylor Morrison, Galveston, Tex.	Thomas Parran
Kenneth Roy Nelson, Baltimore, Md.	Thomas Parran
William Frederick Ossenfort, Fort Worth, Tex.	Thomas Parran
Frank Lewis Price, Ellis Island, N. Y.	Thomas Parran
Edward Clinton Rinck, Lewisburg, Pa.	Thomas Parran
James Raymond Shaw, San Francisco, Calif.	Thomas Parran
James Gavin Telfer, Chicago, Ill.	Thomas Parran
FLORIDA	
Jere Wright Annis, Lakeland	Webster Merritt, William C. Blake, T. Z. Cason
GEORGIA	
Robert Bruce Logue, Atlanta	Carter Smith, H. Cliff Sauls, Glenville Giddings
ILLINOIS	
Harry Allen Warren, Champaign	Lyman H. Hoyt, Soma Weiss, LeRoy H. Sloan
Paul Lawrence Shallenberger, Chicago	Arthur E. Mahle, J. Roscoe Miller, LeRoy H. Sloan
Benjamin Harold Neiman, Oak Park	Maurice Lewison, Isadore M. Trace, LeRoy H. Sloan
IOWA	
John William Grant Caldwell, Des Moines	Daniel J. Glomset, Walter L. Bierring, Fred M. Smith

Associateship Candidates	*Sponsors*
	KANSAS
Lee H. Leger, Kansas City	Fred E. Angle, William H. Algie, Harold H. Jones
	KENTUCKY
James Robert Hendon, Louisville	Frederick G. Speidel, Oscar O. Miller, C. W. Dowden
	LOUISIANA
Norton William Voorhies, New Orleans	Philip H. Jones, Jr., Julius L. Wilson, Joseph E. Knighton
	MASSACHUSETTS
Madelaine Ray Brown, Boston	J. H. Means, Earle M. Chapman, William B. Breed
Milton Henry Clifford, Boston	Wyman Richardson, Thomas V. Urmy, William B. Breed
Eugene Charles Eppinger, Boston	C. Sidney Burwell, Samuel A. Levine, Reginald Fitz, William B. Breed
Charles Folsom Walcott, Cambridge	Conrad Wesselhoeft, James M. Faulkner, William B. Breed
Henry Dows Stebbins, Marblehead	J. H. Means, Walter Bauer, William B. Breed
John Francis McManus, Newton	John A. Foley, Chester S. Keefer, William B. Breed
	MICHIGAN
Charley Johnson Smyth, Eloise	Cyrus C. Sturgis, Herman H. Riecker, Henry R. Carstens
Glenn Edward Drewyer, Flint	Franklin W. Baske, Myrton S. Chambers, Henry R. Carstens
	MINNESOTA
Randall George Sprague, Rochester	Edward H. Rynearson, Samuel F. Haines, Edgar V. Allen
Joseph Maurice Ryan, St. Paul	Harold Edward Richardson, John A. Lepak, Edgar V. Allen
	NEW JERSEY
Joseph Israel Echikson, Newark	Frederic A. Alling, Edward C. Klein, Jr., George H. Lathrope
John Edward Leach, Paterson	Cornelius P. Rhoads, Lloyd F. Craver, C. F. Tenney, George H. Lathrope
Edgar Ernest Evans, Penns Grove	Thomas M. Kain, Ralph K. Hollinshed, George H. Lathrope
Norman Lovell Murray, Summit	Harvey M. Ewing, Dean W. Marquis, George H. Lathrope
Peter James Warter, Trenton	Stanley P. Reimann, John W. Gray, George H. Lathrope
	NEW YORK
Adele Emily Streeseman, Brooklyn	Carl H. Greene, James Alex. Miller, George Morris Piersol, C. F. Tenney
Charles Stewart Wallace, Ithaca	Norman S. Moore, Frederick Beck, Nelson G. Russell
William Chester, Mamaroneck	John L. Kantor, Bernard S. Oppenheimer, C. F. Tenney
Julius Chasnoff, New York	Thomas H. McGavack, Linn J. Boyd, C. F. Tenney
Willis Aloysius Murphy, New York	Asa L. Lincoln, Benjamin I. Ashe, C. F. Tenney
Carl Reich, New York	James R. Lisa, David Stanley Likely, C. F. Tenney
William Dorus Stubenbord, New York	Asa L. Lincoln, Benjamin I. Ashe, C. F. Tenney
Frederick Thomas Zimmerman, New York	Hiland L. Flowers, Charles M. Griffith, C. F. Tenney
John Charles Leonard, Rye	George Blumer, Arthur Bliss Dayton, Charles H. Turkington, C. F. Tenney

Associateship Candidates	*Sponsors*
North Carolina	
William Gardner Morgan, Chapel Hill	W. Reece Berryhill, Groesbeck Walsh, C. H. Cocke
Robert Edwards Stone, Chapel Hill	William deB. MacNider, Tom D. Spies, C. H. Cocke
William Hamilton Roper, Sanatorium	Paul P. McCain, W. Reece Berryhill, C. H. Cocke
Ohio	
Roswell Schiedt Fidler, Columbus	R. W. Kissane, H. V. Weirauk, A. B. Brower
Robert Chester Kirk, Columbus	Jacob Jones Coons, Charles A. Doan, A. B. Brower
Marion Noville Gibbons, Shaker Heights	Harold Feil, Harley A. Williams, A. B. Brower
Oklahoma	
Owen Royce, Jr., Oklahoma City	Wann Langston, E. R. Musick, Lea A. Riely
Oregon	
Vernon Eldred Fowler, Astoria	Ernest L. Boylen, John H. Fitzgibbon, T. Homer Coffen, Homes P. Rush
Frank Perlman, Portland	Robert L. Benson, Noble Wiley Jones, Homer P. Rush
Frank Kenneth Power, Salem	Ernest L. Boylen, T. Homer Coffen, Homer P. Rush
Pennsylvania	
Charles LeRoy Mengel, Allentown	Willard D. Kline, Clyde H. Kelchner, Edward L. Bortz
Louis Clair Burket, Altoona	August S. Kech, Elwood W. Stitzel, R. R. Snowden
Maximo Joseph Tornatore, Clearfield	George A. Ricketts, George McClintock Hutchison, R. R. Snowden
Charles William Smith, Harrisburg	Carl E. Ervin, John B. McAlister, Edward L. Bortz
Robert Pratt McCombs, Philadelphia	George Morris Piersol, Harry Bond Wilmer, Edward L. Bortz
Stoughton Ralph Vogel, Philadelphia	Charles L. Brown, W. Edward Chamberlain, Edward L. Bortz
George Ransom Taylor, Philipsburg	George A. Ricketts, John M. Johnston, R. R. Snowden
Wilton Ross Glenney, Pottsville	Carl E. Ervin, William Devitt, Edward L. Bortz
Texas	
Louie Edgar Allday, Dallas	David W. Carter, Jr., J. Shirley Sweeney, M. D. Levy
John Spurgeon Bagwell, Jr., Dallas	Henry M. Winans, Milford O. Rouse, M. D. Levy
Alfred William Harris, Dallas	David W. Carter, Jr., Soma Weiss, M. D. Levy
Edwin Luther Rippy, Dallas	David W. Carter, Jr., Milford O. Rouse, M. D. Levy
Newton Alvin Kilgore, Jr., Houston	James H. Agnew, John G. Mateer, M. D. Levy
Ralph L. Coffelt, Waco	I. Warner Jenkins, Edward H. Schwab, M. D. Levy
Virginia	
Robley Dunglison Bates, Jr., Richmond	Paul D. Camp, Dean B. Cole, Walter B. Martin
Morton Morris Pinckney, Richmond	Wyndham B. Blanton, William B. Porter, Walter B. Martin
Elam Cooksey Toone, Jr.	William B. Porter, Harry Walker, Walter B. Martin
West Virginia	
Emory Hendon Main, Philippi	Edward J. Van Liere, Raphael J. Condry, Albert H. Hoge
Dominion of Canada	
Ontario	
Robert Williams Graham, Ottawa	Nelson W. Barker, Edgar A. Hines, Jr., Edgar V. Allen, Warren S. Lyman

1942 Postgraduate Courses of the American College of Physicians

In the November, 1941, issue of this journal a full outline of the Program of Postgraduate Courses for 1942 was published. They are repeated here in outline only:

No. 1—ALLERGY

(February 2–14, 1942)

The Roosevelt Hospital, Department of Allergy
New York, N. Y.
Robert A. Cooke, M.D., F.A.C.P., *Director*

This course is registered to capacity and no additional applications can be accepted.

No. 2—THE DIAGNOSIS AND TREATMENT OF HEART DISEASE

(February 2–14, 1942)

Massachusetts General and other Boston Hospitals
Boston, Mass.
Paul D. White, M.D., F.A.C.P., *Director*

No. 3—GENERAL MEDICINE

(February 2–14, 1942)

University of California Medical School and Stanford University School of Medicine, San Francisco, Calif.

William J. Kerr, M.D., F.A.C.P., *Director*
Stacy R. Mettier, M.D., F.A.C.P., *Associate Director*
University of California Medical School

Arthur L. Bloomfield, M.D., F.A.C.P., *Director*
Dwight L. Wilbur, M.D., F.A.C.P., *Associate Director*
Stanford University School of Medicine

This course has been withdrawn due to war concern along the Pacific Coast.

No. 4—INTERNAL MEDICINE

(February 2–14, 1942)

Johns Hopkins University School of Medicine and University of Maryland School of Medicine, Baltimore, Md.

Warfield T. Longcope, M.D., F.A.C.P., *Director*
George W. Thorn, M.D., F.A.C.P., *Associate Director*
Johns Hopkins University School of Medicine

Maurice C. Pincoffs, M.D., F.A.C.P., *Director*
H. Raymond Peters, M.D., F.A.C.P., *Associate Director*
University of Maryland School of Medicine

Although there was a very representative registration for this course, it had to be cancelled due to the fact that the Johns Hopkins Hospital Unit and a number of members of the faculty were called to active military duty, making it both impracticable and impossible to give the course.

No. 5—GASTRO-INTESTINAL DISEASES

(February 2–7, 1942)

Graduate Hospital, University of Pennsylvania
Philadelphia, Pa.
Henry L. Bockus, M.D., F.A.C.P., *Director*

No. 6—ALLERGY
(April 6–18, 1942)
Washington University School of Medicine and
Barnes Hospital, St. Louis, Mo.
HARRY L. ALEXANDER, M.D., F.A.C.P., *Director*

This course has now been withdrawn due to some of the faculty members being called to active military service and it being impossible to get substitutes at so late a date.

No. 7—ARTHRITIS AND RHEUMATIC DISEASES
(April 13–18, 1942)
The Mayo Foundation, University of Minnesota, and
The Mayo Clinic, Rochester, Minn.
PHILIP S. HENCH, M.D., F.A.C.P., *Director*

No. 8—PERIPHERAL VASCULAR DISEASES, INCLUDING HYPERTENSION
(April 6–18, 1942)
The Mayo Foundation, University of Minnesota, and
The Mayo Clinic, Rochester, Minn.
EDGAR V. ALLEN, M.D., F.A.C.P., *Director*

No. 9—GASTRO-INTESTINAL DISEASES
(April 6–18, 1942)
University of Chicago, The School of Medicine
WALTER L. PALMER, M.D., F.A.C.P., *Director*

No. 10—INTERNAL MEDICINE
(April 6–18, 1942)
University of Minnesota Medical School, Minneapolis, Minn.
CECIL J. WATSON, M.D., F.A.C.P., *Director*

For several weeks this course has been filled to capacity and no additional applications can be accepted.

No. 11—TUBERCULOSIS
(April 13–18, 1942)
University of Colorado School of Medicine and Hospitals
Denver, Colo.
JAMES J. WARING, M.D., F.A.C.P., *Director*

A general bulletin announcing these courses was distributed to all members of the College during November, 1941, and a detailed outline of all courses was likewise mailed to all members early in January. It is deeply regretted that war conditions have made it necessary to alter the plans in some respects, as noted in connection with Courses No. 3 and No. 4. War should not be a signal, however, for the end of medical growth, but rather a challenge to greater responsibility for medical progress. Every physician owes it to himself, to his patients and to his country to know more and practice better medicine. Physicians are urged, so far as possible, to keep up their work in postgraduate education.

Reading Lists and Bibliographies

By direction of the Board of Regents the Advisory Committee on Postgraduate Courses of the College attempted to obtain reading lists for each postgraduate course for publication in this journal, making these lists available to the entire membership of the College, in addition to better preparing the men who will take the courses. Several of the Directors after a close and critical study of the texts and articles in the current literature have submitted the lists which follow. In no way are these lists to be considered all inclusive.

Allergy

Course No. 1

Textbooks

Practice of Allergy. Warren T. Vaughan. C. V. Mosby Co., St. Louis, 1939.

Asthma and Hay Fever in Theory and Practice. A. F. Coca, M. Walzer and A. A. Thommen. Charles C. Thomas, Baltimore, 1931.

Clinical Allergy. Louis Tuft. W. B. Saunders Co., Philadelphia, 1937.

Occupational Diseases of the Skin. Louis Schwartz and Louis Tulipan. Lea and Febiger, Philadelphia, 1939.

Monographs

Allergy. C. E. Von Pirquet. Archives of Internal Medicine *7:* 259, 1911.

Anaphylaxis, Hypersensitiveness and Allergy. W. W. C. Topley. An Outline of Immunity, Chapter 12, p. 192. Wm. Wood Co., 1935.

Hypersensitiveness, Anaphylaxis, Allergy. H. Gideon Wells. The Chemical Aspects of Immunity, Chapter 9, p. 225, second edition. Chemical Catalog Co., New York, 1929.

Diseases of Allergy. Robert A. Cooke. Chapter 21, p. 1079, Internal Medicine. John H. Musser. Lea and Febiger, Philadelphia, 1938, third edition.

Diseases of Allergy. Robert A. Cooke. Page 535, A Textbook of Medicine. Russell L. Cecil. W. B. Saunders Co., Philadelphia, 1940, fifth edition.

Human Sensitization. Robert A. Cooke and A. Vander Veer. Journal of Immunology *1:* 201, 1916.

Herter Lectures. H. H. Dale. Bulletin Johns Hopkins Hospital *31:* pps. 257, 310, 373, 1920.

Anaphylaxis. Carl A. Dragstedt. Physiol. Rev. *21:* 563, 1941.

Histamine and Anaphylaxis. W. Feldberg. Annual Review of Physiology, March 1941.

Articles

Immunological Basis of Sensitization

Horse Asthma Following Blood Transfusion. M. A. Ramirez. J. A. M. A. *73:* 984, 1919.

Studies on the Reactions of Asthmatics and on Passive Transference of Hypersusceptibility. Arent de Besche. Am. J. Med. Sciences *166:* 265, 1923.

Indirect Method of Testing. M. Walzer. J. Allergy *1:* 231, 1930.

Studies in Hypersensitiveness. XXXVI. A Comparative Study of Antibodies Occurring in Anaphylaxis, Serum Disease and the Naturally Sensitive Man. Robert A. Cooke and W. C. Spain. J. Immunol. *17:* 295, 1929.

Passive Sensitization of Human Skin by Serum of Experimentally Sensitized Animals. W. B. Sherman, A. Stull and S. F. Hampton. J. Immunology *36:* 447, 1939.

Serological Evidence of Immunity with Co-existing Sensitization in a Type of Human Allergy. Hay Fever. R. A. Cooke, J. H. Barnard, S. Hebald and A. Stull. J. Exper. Med. *62:* 773, 1935.

Immunological Studies of Pollinosis. I. The Presence of Two Antibodies Related to the Same Pollen Antigen in the Serum of Treated Hay Fever Patients. M. H. Loveless. J. Immunol. *38:* 25, 1940.

Studies in the Transmission of Sensitization from Mother to Child in Human Beings. S. D. Bell and Z. Eriksson. J. Immunol. *20:* 447, 1931.

The Placental Transmission of Antibodies in the Skin-Sensitive Type of Human Allergy. W. B. Sherman, S. F. Hampton and R. A. Cooke. J. Exper. Med. *72:* 611, 1940.

The Question of the Elimination of Foreign Protein (Eggwhite) in Woman's Milk. H. H. Donnally. J. Immunol. *19:* 15, 1930.

The Production in the Rabbit of Hypersensitive Reactions to Lens, Rabbit Muscle and Low Ragweed Extracts by the Action of Staphylococcus Toxin. E. L. Burky. J. Allergy *5:* 466, 1934.

General Clinical Allergy

History Taking in Allergic Diseases. F. M. Rackemann. J. A. M. A. *106:* 976, 1936.

Studies in Specific Hypersensitiveness. III. On Constitutional Reactions: The Dangers of the Diagnostic Cutaneous Test and Therapeutic Injection of Allergens. R. A. Cooke. J. Immunol. *7:* 119, 1922.

The Occurrence of Constitutional Reactions in the Treatment of Hay Fever and Asthma: Analysis of the Causative Factors. F. F. Furstenberg and L. N. Gay. Bull. Johns Hopkins Hospital *60:* 412, 1937.

The Delayed Type of Allergic Reaction. R. A. Cooke. Ann. Int. Med. *3:* 658, 1930.

Treatment of Allergic Disorders with Histamine and Histaminase. H. L. Alexander. J. Lab. & Clin. Med. *26:* 110, 1940.

Asthma

Asthma in Children. R. A. Cooke. J. A. M. A. *102:* 664, 1934.

Infective Asthma. Indication of Its Allergic Nature. R. A. Cooke. Am. J. Med. Sci. *183:* 309, 1932.

Relation of Asthma to Sinusitis with Special Reference to the Results from Surgical Treatment. R. A. Cooke and R. C. Grove. Arch. Int. Med. *56:* 779, 1935.

The Pathology of Bronchial Asthma. H. L. Huber and K. K. Koessler. Arch. Int. Med. *30:* 689, 1922.

Effects on Heart of Long Standing Bronchial Asthma. H. L. Alexander, D. Luten and W. B. Kountz. J. A. M. A. *88:* 882, 1927.

Deaths from Bronchial Asthma. W. B. Kountz and H. L. Alexander. Arch. Path. *5:* 1003, 1928.

Studies in Specific Hypersensitiveness. IV. New Etiologic Factors in Bronchial Asthma. R. A. Cooke. J. Immunol. *7:* 147, 1922.

Asthma Due to a Fungus-Alternaria. J. G. Hopkins, R. W. Denham and B. M. Kesten. J. A. M. A. *94:* 6, 1930.

Nasal Allergies

Seasonal Hay Fever and Asthma Due to Molds. S. M. Feinberg. J. A. M. A. *107:* 1861, 1936.

Importance of Allergy in Etiology and Treatment of Nasal Mucous Polyps. R. A. Kern. J. A. M. A. *103:* 1293, 1934.

The Preparation and Standardization of Pollen Extracts for the Treatment of Hay Fever. R. A. Cooke and A. Stull. J. Allergy *4:* 87, 1933.

New Plan for Applying Specific Treatment of Pollen Hay Fever (Perennial Treatment). Aaron Brown. J. Immunol. *13:* 273, 1927.

The Relative Merits of Seasonal and Perennial Treatment of Hay Fever. A. Vander Veer. J. Allergy *7:* 578, 1936.

Calculating Pollen Concentration of the Air. E. C. Cocke. J. Allergy *8:* 601, 1937.

Evaluation of the Ragweed Hay Fever Resort Areas of North America. O. C. Durham. J. Allergy *8:* 175, 1937.

Intestinal Allergy

Gastro-intestinal Manifestations of Allergy. R. A. Cooke. Bull. N. Y. Acad. Med. Second Series *IX:* 15, 1933.

Food Idiosyncrasy as a Factor of Importance in Gastro-enterology and in Allergy. W. T. Vaughan. Rev. Gastroenterol. *5:* 1, 1938.

Skin Allergy

A Tentative Classification of Allergic Dermatoses. M. B. Sulzberger, F. Wise and J. Wolf. J. A. M. A. *104:* 1489, 1935.

A Critical Review of 170 Cases of Urticaria and Angioneurotic Edema Followed for a Period of from Two to Ten Years. A. I. Fink and L. N. Gay. J. Allergy *5:* 615, 1934.

Eczema. L. W. Hill. Vol. IV., Chapter 43, Brenneman's Practice of Pediatrics. W. F. Prior Co., Hagerstown, Md.

Studies in Specific Hypersensitiveness. XXVII. Dermatitis Venenata: Toxicodendron Radicans. W. C. Spain and R. A. Cooke. J. Immunol. *13:* 93, 1927.

Report of the Investigation and Successful Treatment (Preventive) of Dermatitis Resulting from the Handling of Tulip Bulbs. A. H. W. Caulfeild. J. Allergy *8:* 181, 1937.

Miscellaneous Allergy

Cerebral Symptoms Induced by Angioneurotic Edema. F. Kennedy. Arch. Neurol. and Psychiat. *15:* 28, 1926.

Allergic Migraine. W. T. Vaughan. J. A. M. A. *88:* 1983, 1927.

Food Allergy in Henoch's Purpura. H. L. Alexander and C. H. Eyermann. Arch. Dermat. & Syph. *16:* 332, 1927.

The Clinical Diagnosis of Periarteritis Nodosa. M. B. Cohen, B. S. Kline and A. M. Young. J. A. M. A. *107:* 1555, 1936.

Allergy Induced by Immunization with Tetanus Toxoid. R. A. Cooke, S. F. Hampton, W. B. Sherman and A. Stull. J. A. M. A. *114:* 1854, 1940.

Elimination of Horse Serum Specificity from Antitoxins. R. D. Coghill, N. Fell, M. Creighton and G. Brown. J. Immunol. *39: 207*, 1940.

Physical Allergy. W. W. Duke. J. A. M. A. *84: 736*, 1925.

Allergy in Drug Idiosyncrasy. R. A. Cooke. J. A. M. A. *73: 759*, 1919.

THE DIAGNOSIS AND TREATMENT OF HEART DISEASE

COURSE NO. 2

Tandler, J. Anatomie des Herzens, Gustav Fischer, Jena, 1913.

Wiggers, C. J. Physiology in Health and Disease. 3rd edition. Lea & Febiger, Philadelphia, 1939.

Lewis, Thomas. The Mechanism and Graphic Registration of the Heart Beat, Shaw and Sons, London, 1925.

Blood, Heart, and Circulation. Publication of American Association for Advancement of Science, No. 13, Science Press, Washington, D. C., 1940.

Henke, F. and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie, Julius Springer, Berlin, 1924.
A. Mönckeberg, J. G. and Ribbert, Hugo.
On the Heart.
B. Jores, L.
On Arteries.
C. Benda, C.
On Veins.
Ashman, R. and Hull, E. Essentials of Electrocardiography for the Student and Practitioner of Medicine, second edition, The Macmillan Co., New York, 1941.
Pardee, H. Clinical Aspects of the Electrocardiogram including the Cardiac Arrhythmias, 4th edition. Paul Hoeber, New York, 1941.
Barnes, Arlie. Electrocardiographic Patterns. C. C. Thomas, Springfield, Ill., and Baltimore, Md., 1940.
Graybiel, A., and White, P. D. Electrocardiography in Practice, W. B. Saunders Co., Philadelphia, 1941.
Roesler, Hugo. Clinical Roentgenology of the Cardiovascular System. C. C. Thomas, Springfield, Ill. and Baltimore, Md., 1937.
Roesler, Hugo. Atlas of Roentgenology. C. C. Thomas, Springfield, Ill. and Baltimore, Md., 1940.
Laubry, Ch., et al. Radiologie clinique du coeur et des gros Vaisseux, Masson et Cie, Paris, 1939.
Lewis, Thomas. Diseases of the Heart, 2nd edition. The Macmillan Company, New York, 1937.
White, Paul D. Heart Disease, 2nd edition. The Macmillan Company, New York, 1937.
Levine, Samuel. Clinical Heart Disease, 2nd edition, W. B. Saunders Co., 1940.
Stroud, William D. Diagnosis and Treatment of Cardiovascular Disease, 2 volumes. F. A. Davis Company, Philadelphia, Pa., 1940.
Herrmann, George R. Synopsis of Diseases of the Heart and Arteries, 2nd edition. C. V. Mosby Co., St. Louis, 1941.
Levy, Robert. Diseases of the Coronary Arteries and Pain. The Macmillan Company, New York, N. Y., 1936.
Fishberg, A. M. Heart Failure. Lea & Febiger, Philadelphia, 1937.
Harrison, T. R. Failure of the Circulation, 2nd edition. Williams and Wilkins Company, Baltimore, Md., 1939.
Homans, John. Circulatory Diseases of the Extremities. The Macmillan Company, New York, N. Y., 1939.
Leaman, William G., Jr. Management of the Cardiac Patient. J. B. Lippincott Company, Philadelphia, 1940.

GASTRO-INTESTINAL DISEASES

COURSE No. 5

Liver Function

Mann, F. C.: The Liver and Medical Progress, J. A. M. A., *117:* 1577 (Nov. 8) 1941.
Bockus, H. L., and Tumen, H. J.: Jaundice, The Cyclopedia of Medicine, Surgery and Specialties, Philadelphia, F. A. Davis Co. *8:* 168–205, 1939.
Ravdin, I. S.: The Protection of the Liver from Injury, Surgery, *8:* 204–211 (Aug.) 1940.
Epstein, E. Z., and Greenspan, E. D.: Clinical Significance of Cholesterol Partition of the Blood Plasma in Hepatic and Biliary Diseases, Arch. Int. Med. *58:* 860, 1936.

Lehnherr, E. R.: The Value of the Icteric Index and Plasma Lipids in the Diagnosis of Jaundice, New Eng. J. Med. *211:* 487–492 (Sept. 14) 1934.

Sperry, W. M.: The Relationship Between Total and Free Cholesterol in Human Blood Serum, J. Biol. Chem. *114:* 125–131 (May) 1936.

Block, W. D., Buchanan, M. S., and Freyberg, R. H.: Serum Lipids in Rheumatoid Arthritis and in Patients with Obstructive Jaundice, Arch. Int. Med., *68:* 18 (July) 1941.

Tumen, H., and Bockus, H. L.: The Clinical Significance of Serum Proteins in Hepatic Diseases, Am. J. Med. Sci. *193:* 788 (June) 1937.

Quick, A. J.: The Nature of the Bleeding in Jaundice, J. A. M. A., *110:* 1658 (May 14) 1938.

Stewart, J. D.: Clinical Significance of Prothrombin Deficiency and Its Treatment, Ann. Surg., *114:* 907–918 (Nov.) 1941.

Rhoads, J. E., Warren, R., and Panzer, L. M.: Experimental Hypoprothrombinemia, Am. J. Med. Sci., *202:* 847–861 (Dec.) 1941.

Rothman, M. M., Meranze, D. R., and Meranze, T.: Blood Phosphatase as an Aid in the Differential Diagnosis of Jaundice, Am. J. Med. Sci., *192:* 526 (Oct.) 1936.

Woodward, H. Q., and Higinbotham, N. L.: Serum and Tissue Phosphatase Determinations, J. A. M. A. *116:* 1621 (Apr. 12) 1941.

Shay, H., and Fieman, P.: The Galactose Tolerance Test in Jaundice, Ann. Int. Med. *10:* 1297 (Mar.) 1937.

Tumen, H. J., and Piersol, G. M.: The Value of Alimentary Galactosuria in the Diagnosis of Jaundice, Ann. Int. Med. *12:* 311–329 (Sept.) 1933.

Shay, H. and Fieman, P.: The Value of a Combined Study of the Newer Laboratory Tests in the Differential Diagnosis of Toxic and Obstructive Jaundice, Including Blood Phosphatase, Cholesterol Partition, Galactose Tolerance and Glucose Tolerance, Am. J. Dig. Dis. *5:* 597 (Nov.) 1938.

Rosenberg, D. N.: Cephalin-Cholesterol Flocculation Test, Arch. Surg. *43:* 231 (Aug.) 1941.

Snell, A. M., and Magath, T. B.: The Use and Interpretation of Tests for Liver Function, J. A. M. A. *110:* 167 (Jan. 15) 1938.

Chronic Gastritis

Monaghan, J. F., Bockus, H. L., Kornblum, K. and Moffit, G. R.: Gastric Secretory Behavior in Chronic Gastritis, Am. J. Dig. Dis. *3:* 655 (Nov.) 1936.

Schindler, R.: Gastroscopy, Univ. of Chicago Press, 1937.

Ansprenger, A., and Kirklin, B. R.: Roentgenologic Aspects of Chronic Gastritis, Am. J. Roentgenol. and Rad. Ther. *38:* 533, 1937.

Golden, R.: Antral Gastritis and Spasm, J. A. M. A. *109:* 1497, 1937.

Johnson, T. A.: Acute and Chronic Gastritis, Tice Practice of Medicine, W. F. Prior Co. Inc., Vol. VII, p. 417–432.

Jones, C. M.: Clinical Evaluation of Gastritis, Am. J. Dig. Dis. *8:* 205 (June) 1941.

Tumen, H. J., and Lieberthal, M. M.: Chronic Gastritis: A Review of the Present Status, New International Clinics, Philadelphia, J. B. Lippincott Co., 1941, Vol. 2, pp. 263–291.

Swalm, W. A., and Morrison, L. M.: Gastroscopic and Histologic Studies of the Stomach with Gastric and Extragastric Diseases During Life and at Autopsy, Am. J. Digest. Dis. *8:* 391–397 (Oct.) 1941.

Clinical Demonstrations

Bockus, H. L., Shay, H., Willard, J. H., and Pessel, J. F.: Comparison of Biliary Drainage and Cholecystography, Gallstone Diagnosis, J. A. M. A. *96:* 311 (Jan. 31) 1931.

Rousselot, L. M., and Bauman, L.: Cholesterol Crystals and Calcium Bilirubinate Granules: Their Significance in Bile Obtained through the Duodenal Tube, J. A. M. A. *100:* 254–256 (Jan. 28) 1933.

Craig, C. F., and Faust, E. C.: Clinical Parasitology, Lea and Febiger, Philadelphia, 1940.

Esophagus

Tucker, Gabriel: Diseases of the Esophagus: Diagnosis and Treatment: Esophagoscopic Observations, Proceedings of the Inter-State Postgraduate Medical Assembly of North America, October 1935, Detroit, Michigan.

Tucker, G., and Thigpen, F. M.: Esophageal Diverticulum, with Report of 10 Cases of Pulsion Type Originating in Pharynx, Surgery, *2:* 188 (Aug.) 1937.

Tucker, Gabriel: Cicatricial Stenosis of the Esophagus with Particular Reference to Treatment by Continuous String Retrograde Bouginage with the Author's Bougie. (Report of twenty-five cases), Transactions of the 30th Annual Meeting of the American Laryn., Rhinol. and Otol. Society, 1924.

Nutritional Deficiencies and Gastro-intestinal Disorders

Elsom, K. O., Lukens, F. D. W., Montgomery, E. H., and Jonas, L.: Metabolic Disturbances in Experimental Human Vitamin B Deficiency, J. Clin. Investigation, *19:* 153 (Jan.) 1940.

Elsom, K. O., Lewy, F. H., and Heublein, G. W.: Clinical Studies of Experimental Human Vitamin B Complex Deficiency, Am. J. M. Sc. *200:* 757 (Dec.) 1940.

Mackie, T. T., and Pound, R. E.: Changes in the Gastro-intestinal Tract in Deficiency States, J. A. M. A. *104:* 613, 1935.

Bennett, T. I., Hunter, D., and Vaughan, J. M.: Idiopathic Steatorrhea (Gee's Disease), A Nutritional Disturbance Associated with Tetany, Osteomalacia and Anemia, Quart. J. Med. *1:* 603, 1932.

Thaysen, T. E. H.: Ten Cases of Idiopathic Steatorrhea, Quart. J. Med. *4:* 359, 1935.

Snell, A. M., and Camp, J. O.: Chronic Idiopathic Steatorrhea: Roentgenologic Observations, Arch. Int. Med. *53:* 615, 1934.

Verzar, F., and McDougall, E. J.: Absorption from the Intestine, London, Longmans, Green and Co. 1936.

Golden, R.: The Small Intestine and Diarrhea, Am. J. Roent. *36:* 892 (Dec.) 1936.

Kirklin, B. R., and Weber, H. M.: Roentgenologic Diagnosis of Diseases of the Small Intestine, Am. J. Dig. Dis. *7:* 475 (Nov.) 1940.

Golden, Ross: Nutritional Disturbances of the Small Bowel, Radiology *36: 262,* (March) 1941.

Functional Disorders of the Gastro-intestinal Tract

Dunbar, F.: Emotions and Bodily Changes: A Report of Some Recent Psychosomatic Studies, Ann. Int. Med. *14:* 839 (Nov.) 1940.

McCullagh, E. P., and Tupper, W. R.: Anorexia Nervosa, Ann. Int. Med. *14:* 817 (Nov.) 1940.

White, B. V., and Jones, C. M.: Mucous Colitis: A Delineation of the Syndrome with Certain Observations on its Mechanism and on the Rôle of Emotional Tension as a Precipitating Factor, Ann. Int. Med. *14:* 854 (Nov.) 1940.

Bockus, H. L.: The Irritable Colon: Diagnosis and Treatment, Med. Clinics No. America, July, 1937.

Gray, I., Harten, M., and Walzer, M.: Studies in Mucous Membrane Hypersensitiveness; Allergic Reaction in Passively Sensitized Mucous Membranes of Ileum and Colon in Humans, Ann. Int. Med. *13:* 2050 (May) 1940.

Conn, J. W.: The Spontaneous Hypoglycemias, J. A. M. A. *115:* 1669 (Nov. 16) 1940.

Regional Enteritis and Enterocolitis

Crohn, B. B., Ginsburg, L., and Oppenheimer, G. D.: Regional Ileitis, J. A. M. A. *99:* 1323 (Oct. 15) 1932.

Marshall, S. F.: Regional Ileitis, New Eng. J. Med., *222:* 375 (Mar. 7) 1940.

Bockus, H. L., Johnson, T. A., and Lee, W. E.: Appraisal of Results of Surgically Treated Chronic Regional Ileitis. Lahey Birthday Vol., pp. 53–83, 1940.

Pancreatic Disorders

Johnson, T. A., and Bockus, H. L.: Diagnostic Significance of Determinations of Serum Lipase, Arch. Int. Med. *66:* 62 (July) 1940.

Dozzi, D. L.: Urinary Amylase: Its Estimation and Significance, Am. Dig. Dis. *7:* 123 (Mar.) 1940.

Berk, J. E.: Diagnosis of Carcinoma of the Pancreas, Arch. Int. Med. *68:* 525 (Sept.) 1941.

Peptic Ulcer

Feigenbaum, J., and Howat, D.: The Relation Between Physical Constitution and the Incidence of Disease, J. Clin. Invest. *13:* 121, 1934, Arch. Int. Med. *55:* 445, 1935.

Necheles, H.: A Theory on the Formation of Peptic Ulcer, Am. J. Digest. Dis. *4:* 643 (Dec.) 1937.

Boles, R. S., Riggs, H. E., and Griffiths, J. O.: The Rôle of the Circulation in the Production of Peptic Ulcer, Am. J. Digest. Dis. *6:* 632 (Nov.) 1939.

Sandweiss, D. J., Saltzstein, H. C., and Farbman, A. A.: The Relation of Sex Hormones to Peptic Ulcer, Am. J. Digest. Dis. *6:* 6 (March) 1939.

Vanderahe, A. R.: Histopathologic Changes in the Nervous System in Cases of Peptic Ulcer, Arch. Neur. and Psychiatry *41:* 871 (May) 1939.

Quigley, J. P.: Enterogastrene, Significant Steps in Development of the Present Conceptions, Am. J. Digest. Dis. *8:* 363 (Oct.) 1941.

Gray, J. S.: Present Status of Urogastrone, Am. J. Digest. Dis. *8:* 365 (Oct.) 1941.

Palmer, W. L., and Nutter, P. B.: A Further Study of the Rôle of Acid Gastric Juice in the Pathogenesis of Peptic Ulcer, Arch. Int. Med. *65:* 499 (Mar.) 1940.

Cole, L. G.: Anatomical Factors Predisposing to Corporic Ulcer, New Eng. Jour. Med. *201:* 1081 (Nov. 28) 1929.

Palmer, W. L.: Benign and Malignant Gastric Ulcers: Their Relation and Clinical Differentiation, Ann. Int. Med. *13:* 317 (Aug.) 1939.

Ravdin, I. S., Stengel, A., Jr., and Prushankin, M.: The Control of Hypoproteinemia in Surgical Patients, J. A. M. A. *114:* 107 (Jan. 13) 1940.

Lahey, F. H.: Diagnosis and Management of Gastrojejunal Ulcer and Gastrojejunocolic Fistula, S. Clin. North America *20: 767* (June) 1940.

Jordan, S. M.: End Results of Radical Surgery of the Gastro-intestinal Tract as Seen by the Gastro-enterologist, J. A. M. A. *116:* 586 (Feb. 15) 1941.

Jones, C. M.: The Problem of Gastrectomy and the Anemias, Am. J. Digest. Dis. *7:* 502 (Nov.) 1940.

Miller, T. G.: Management of Complications of Peptic Ulcer, New Eng. J. Med. *224:* 401 (Mar. 6) 1941.

Nicholson, J. T. L., and Miller, T. Grier: The Prompt Feeding Program for Bleeding Gastric and Duodenal Ulcer, Am. J. Dig. Dis. *8:* 446 (Dec.) 1941.

Ravdin, I. S., and Johnston, C. G.: Some Observations on Perforated Gastric and Duodenal Ulcer, Am. J. Med. Sci. *200:* 275 (Aug.) 1940.

Achlorhydria

Bockus, H. L., Bank, J., and Willard, J. H.: Achlorhydria: with a Review of 210 Cases in Patients with Gastro-intestinal Complaints, Am. J. Med. Sci. *184:* 185 (Aug.) 1932.

Davies, D. T., and James, T. G. I.: Lancet, *2:* 899, 1930.

Dameshek, W.: Chronic Hypochromic Anemia, Cyclopedia of Medicine, Surgery and Specialties, Philadelphia, F. A. Davis Co. 1939, Vol. 2, p. 736.

Heath, C. W.: Anemia Due to Iron Deficiency, A Symposium on the Blood and Blood-forming Organs, University of Wisconsin Press, 1939, p. 41.

Minot, G. R.: Anemias of Nutritional Deficiency, A Symposium on the Blood and Blood-forming Organs, University of Wisconsin Press, 1939, p. 52.

Meulengracht, E.: Some Etiological Factors in Pernicious Anemia, A Symposium on the Blood and Blood-forming Organs, University of Wisconsin Press, 1939, p. 72.

Miscellaneous

Abbott, W. O., and Johnston, C. G.: Intubation Studies of the Human Small Intestine, Surg., Gyn. and Obstet. *66:* 691 (Apr.) 1938.

Jones, C. M.: Gastro-enterology, A Review of Literature from July 1940 to July 1941, Arch. Int. Med. *68:* 763 (Oct.) 1941.

Jones, C. A.: A Clinical and Laboratory Study of Plasma Lipids in Obstructive Jaundice and Several Types of Hepatic Disease, Amer. Jr. Dig. Dis. *9:* 1–13, January, 1942.

ARTHRITIS AND RHEUMATIC DISEASES

COURSE NO. 7

Hench, Philip S.; Bauer, Walter; Dawson, M. Henry; Hall, Francis; Holbrook, W. Paul; Key, J. Albert; and McEwen, Currier. The Problem of Rheumatism and Arthritis; Review of American and English Literature for 1939.

Seventh Rheumatism Review, Part I; Ann. Int. Med., *14:* 1383, (Feb.) 1941.
Part II; Ann. Int. Med., *14:* 1631, (March) 1941.

Review of American and English Literature for 1940.

Eighth Rheumatism Review, Part I; Ann. Int. Med., *15:* 1002, (Dec.) 1941.
Part II; Ann. Int. Med., *16:* , (Jan.) 1942.

(Note: The preceding reviews, First to Sixth inclusive, also appeared in the Annals of Internal Medicine, one review each year, from 1935 forward.)

PERIPHERAL VASCULAR DISEASES, INCLUDING HYPERTENSION

COURSE NO. 8

1. Ochsner, Alton and Mahorner, Howard: Varicose Veins. C. V. Mosby Co. St. Louis. 1939.
2. Herrmann, Louis G.: Passive Vascular Exercise. J. B. Lippincott Co. Philadelphia. 1936.
3. Samuels, Saul S.: The Diagnosis and Treatment of Diseases of the Peripheral Arteries. Oxford University Press. New York. 1936.
4. Brown, George E., Allen, E. V. and Mahorner, Howard: Thrombo-angiitis Obliterans. W. B. Saunders Co. Philadelphia. 1928.
5. Collens, William S. and Wilansky, Nathan D.: Peripheral Vascular Diseases. Charles C. Thomas. Springfield, Illinois. 1939.

X6. Kvale, Walter F. and Allen, E. V.: The Rate of Circulation in the Arteries and Veins of Man. Am. Heart J. *18:* 519–536; 546–556; 557–561. (Nov.) 1939.
X7. Scupham, George W., deTakats, Geza, VanDellen, T. R. and Beck, W. C.: Vascular Diseases; a Review of Some of the Recent Literature with a Critical Review of the Surgical Treatment. Arch. Int. Med. *64:* 590–655 (Sept.) 1939.
X8. Wright, I. S.: The Treatment of Arteriosclerosis Obliterans; Social Significance and Ultimate Objective. J. A. M. A. *115:* 893–895 (Sept. 14) 1940.
X9. Wright, I. S.: Physical Therapy in Peripheral Vascular Disease. Arch. Phys. Therapy *19:* 161–172 (Mar.) 1938.
X10. Holman, Emile: Clinical and Experimental Observations on Arteriovenous Fistulae. Ann. Surg. *112:* 840–875 (Nov.) 1940.
11. Barker, N. W.: Results of Treatment of Thrombo-angiitis Obliterans by Foreign Protein. J. A. M. A. *97:* 841–843 (Sept. 19) 1931.
X12. Barker, N. W.: General Classification of Diseases of Veins and Clinical Types of Thrombophlebitis. Proc. Staff Meet., Mayo Clin. *9:* 191–194 (Mar. 28) 1934.
X13. Barker, N. W.: Diseases of the Veins. M. Clin. North America *19:* 535–543 (Sept.) 1935.
14. Chew, E. M., Allen, E. V. and Barker, N. W.: Orthostatic Hypotension: a Report of Six Cases and Review of the Literature. Northwest Med. *35:* 297–303 (Aug.) 1936.
15. Goldblatt, Harry: Studies on Experimental Hypertension: the Pathogenesis of Experimental Hypertension due to Renal Ischemia. Ann. Int. Med. *11:* 69–103 (July) 1937.
16. Page, I. H.: Newer Aspects of Experimental Hypertension. American Association for the Advancement of Science. Publication 13, pp. 239–265.
17. Weiss, Soma: Recent Advances in the Treatment of Arterial Hypertension. Med. Clin. North America 1343–1365 (Mar.) 1936.
18. Barker, M. H.: The Use of Cyanates in the Treatment of Hypertension. Wisconsin M. J. (Jan.) 1937.
19. Barker, M. H.: The Blood Cyanates in Treatment of Hypertension. J. A. M. A. *106:* 762–767 (Mar. 7) 1936.
X20. Allen, E. V. and Adson, A. W.: The Treatment of Hypertension; Medical versus Surgical. Ann. Int. Med. *14:* 288–307 (Aug.) 1940.
21. Adson, A. W.: Surgical Treatment of Peripheral Vascular Diseases. Proc. Interstate Post-Graduate Med. Assoc. of North America. 196–199, 1940.
22. Craig, W. McK. and Smith, H. L.: The Surgical Treatment of Hypersensitive Carotid Sinus Reflexes. A report of thirteen cases. J. Biology and Medicine *11:* 415–422 (Mar.) 1933.
X23. Craig, W. McK.: Hypertension and Consideration of Its Surgical Treatment. Brit. M. J. *2:* 1215–1219 (Dec. 23) 1939.
24. MacLean, A. R. and Allen, E. V.: Orthostatic Hypotension and Orthostatic Tachycardia: Treatment with "Head-up" Bed. J. A. M. A. *115:* 2162–2167 (Dec. 21) 1940.
X25. Hines, E. A.: Variability of the Blood Pressure. Virginia Med. Monthly *67:* 757–759 (Dec.) 1940.
X26. Hines, E. A.: The Significance of Vascular Hyper-reaction as Measured by the Cold-pressor Test. Am. Heart J. *19:* 408–416 (Apr.) 1940.
X27. Hines, E. A. and Barker, N. W.: Arteriosclerosis Obliterans: a Clinical and Pathologic Study. Am. J. M. Sc. *200:* 717–730 (Dec.) 1940.
X28. Keith, N. M., Wagener, H. P. and Barker, N. W.: Some Different Types of Essential Hypertension: Their Course and Prognosis. Am. J. M. Sc. *197:* 332–343 (Mar.) 1939.

29. Smith, L. A. and Allen E. V.: Erythromelalgia (Erythrothermalgia) of the Extremities; a Syndrome Characterized by Redness, Heat, and Pain. Am. Heart J. *16:* 175–188 (Aug.) 1938.
30. McKechnie, R. E. and Allen, E. V.: Sudden Occlusion of the Arteries of the Extremities: Study of 100 Cases of Embolism and Thrombosis. Surg., Gynec. and Obst. *63:* 230–240 (Aug.) 1936.
31. Allen, E. V. and Ghormley, R. K.: Lymphedema of the Extremities. Etiology, Classification, and Treatment; Report of 300 Cases. Arch. Int. Med. *54:* 606–624 (Oct.) 1934.
32. Scott, R. W.: Hypertension a Century After Bright. J. A. M. A. *3:* 2460–2463 (Dec. 31) 1938.
33. Wiggers, C. J.: Mechanisms of Peripheral Circulatory Failure. Ann. Int. Med. *15:* 178–189 (August) 1941.
34. Page, I. H., and associates: Reduction of Arterial Blood Pressure with Extracts of Kidney. Jour. Exper. Med., *73:* 7–41 (January) 1941.

X—Checked in the Cumulative Index Medicus.

Gastro-intestinal Diseases

Course No. 9

Books

Portis: Diseases of the Digestive System.
Eusterman and Balfour: Stomach and Duodenum.
Walters and Snell: Diseases of the Gall Bladder and Biliary Tract.
Alvarez: Nervous Indigestion.
Schindler: Gastroscopy: The Endoscopic Study of Gastric Pathology.
Berg, H. H.: Roentgenuntersuchungen am innenrelief des vergauungskanals.
Livingston and Pack: Prognosis of Gastric Carcinoma.
Bloomfield and Polland: Gastric Anacidity.
Rankin, Bargen, and Buie: The Colon, Rectum, and Anus.
Craig: Amoebiasis and Amoebic Dysentery.

Articles

Ivy, A. C.: Some Recent Advances in the Physiology of the Alimentary Tract, Am. J. Digest. Dis. *8:* 361, 1941.
Jones, C. M.: Medical Progress: Treatment of Biliary Tract Disease, New Eng. J. Med. *224:* 509, 1941.
Jones, C. M.: Progress in Internal Medicine: Gastro-enterology. A Review of Literature from July, 1940, to July, 1941, Arch. Int. Med. *68:* 763, 1941.

Internal Medicine

Course No. 10

Blood

Bell: Textbook of Pathology.
Maximow-Bloom: Text Book of Histology.
Downey: Handbook of Hematology.
Ewald, O.: Die leukamische Retikuloendotheliose. Deutsches Arch. f. klin. Med. *142:* 222, 1923.
Clough, P. W.: Monocytic Leukemia. Johns Hopkins Hospital Bulletin *51:* 148, 1932.
Downey, Hal: Monocytic Leukemia and Leukemic Reticuloendotheliosis. Handbook of Hematology. 1274–1329. Paul B. Hoeber, New York. 1938.

The 1941 Yearbook of Pathology and Immunology, pages 499–513.
Levine, Philip: Am. J. Clin. Path. *11:* 898, 1941.
Levine, Burnham, Katzin, and Vogel: Am. J. Obs. and Gynec. *42:* 925, 1941.
Watson, C. J.: Hemolytic Jaundice, Etc. Ann. Int. Med. *12:* 1782, 1939.
Castle, W. B., and Minot, G. R.: Pathological Physiology and Clinical Description of the Anemias. Oxford Med. pp. 18, 23–117. 1936.
Ham, Thomas Hale, and Castle, William B.: Studies on Destruction of Red Blood Cells: Relation of Increased Hypotonic Fragility and of Erythrostasis to the Mechanism of Hemolysis in Certain Anemias. Reprinted from Proceedings of the American Philosophical Society *82:* No. 4, 1940.
Rosenthal, N.: Hemorrhagic Diathesis. In Downey's Handbook of Hematology. Sect. VIII. Paul Hoeber, 1938.

Liver and Biliary Tract

Martin, L.: Jaundice. Internat. Clinics *1:* 19, 1934.
Weir, J. F., and Parch, W. J.: The Relationship of Pain to Jaundice. Ann. Int. Med. *4:* 1509, 1931.
Bassett, A. M., Althausen, T. L., and Coltrin, G. C.: A New Galactose Test for Differentiation of Obstructive from Parenchymatous Jaundice. Am. J. Dig. Dis. *8:* 432, 1941.
Watson, C. J.: Diseases of the Gall Bladder and Biliary Tract. In Cecil's Textbook of Medicine. 5th Edition. Saunders & Company. 1940.
Watson, C. J.: Pyrrol Pigments. In Downey's Handbook of Hematology. v. IV. Paul Hoeber and Co. 1938.
Lord, J. W., and Andrus, W. D.: Differentiation of Intrahepatic and Extra Hepatic Jaundice: Response of Plasma Prothrombin to Intramuscular Infection of 2-Methyl, 1, 4 Naphtho Quinone, as Diagnostic Aid. Arch. Int. Med. *68:* 199, 1941.
Patek, A. J., and Post, J.: Treatment of Cirrhosis of the Liver by a Nutritious Diet and Supplements Rich in Vitamin B Complex. J. Clin. Investig. *20:* 481, 1941.
Thompson, William P., Caughey, John L., Whipple, Allen O., and Rousselot, Louis M.: Splenic Vein Pressure in Congestive Splenomegaly (Banti's Syndrome). Reprinted from J. Clin. Investig. *16:* No. 4 (July) 1937.
Snell, Albert M.: Recent Advances in Treatment of Hepatic Disease. Reprinted from Minnesota Medicine *23:* 551 (August) 1940.
Rousselot, Louis M.: The Late Phase of Congestive Splenomegaly (Banti's Syndrome) with Hematemesis but without Cirrhosis of the Liver. Reprinted from Surgery *8:* No. 1, 34–42 (July) 1940.
White, Franklin W., Deutsch, Emmanuel, Maddock, Stephen: The Comparative Value of Serial Hippuric Acid Excretion, Total Cholesterol, Cholesterol Ester and Phospho-Lipid Tests in Diseases of the Liver: Clinical Comparison of the Tests. Reprinted from The American Journal of Digestive Diseases *7:* No. 1, 3–7 (January) 1940.
White, Franklin W., Deutsch, Emmanuel, and Maddock, Stephen: The Comparative Value of Serial Hippuric Acid Excretion, Total Cholesterol, Cholesterol Ester and Phospho-Lipid Tests in Diseases of the Liver: The Results of the Tests. Reprinted from the American Journal of Digestive Diseases *6:* No. 9, 603–610 (November) 1939.
Watson, C. J.: Regurgitation Jaundice. J. A. M. A. *114:* 2427, 1940.
White, Franklin W.: The Galactose Tolerance and Urobilinogen Tests in the Differential Diagnosis of Painless Jaundice. Reprinted from the American Journal of Digestive Diseases and Nutrition *4:* No. 5 (July) 315–325.

Metabolism and Endocrinology

Means, J. H.: The Thyroid and Its Diseases. Chapt. VIII, X, XIV. J. B. Lippincott Co., Phila., 1937.

Althausen, T. L.: The Disturbance of Carbohydrate Metabolism in Hyperthyroidism. J. A. M. A. *115:* 101, 1940.

Althausen, T. L., Lockhart, J. C., and Soley, M. H.: A New Diagnostic Test (Galactose) for Thyroid Disease. Am. J. Med. Sci. *199:* 342, 1940.

Bauer, W., and Camp, J. D.: Malacic Diseases of Bone. In Nelson's New Looseleaf Surgery. Thomas Nelson & Sons, New York, *3:* 175N–177C, 1937.

Camp, J. D.: Roentgenologic Changes in Malacic Diseases of Bone. Radiology *26:* 399–408 (April) 1936.

Jaffe, H. L.: Resorption of Bone; a Consideration of the Underlying Processes Particularly in Pathologic Conditions. Arch. Surgery *20:* 355–385 (March) 1930.

Hunter, Donald: Studies in Calcium and Phosphorus Metabolism in Generalized Diseases of Bones. Proc. Roy. Soc. Med. *28:* 1619–1638 (October) 1935.

Eighth Rheumatism Review: Annals of Internal Medicine. December, 1941.

Hench, P. S.: The Diagnosis and Treatment of Gout and Gouty Arthritis. Journal A. M. A. February 8, 1941.

Ludwig, A. O., Bennett, G. A., and Bauer, Walter: A Rare Manifestation of Gout; Widespread Ankylosis Simulating Rheumatoid Arthritis. Annals of Internal Medicine. January, 1938.

McQuarrie, Irvine, Johnson, R. M., and Ziegler, M. R.: Plasma Electrolyte Disturbance in Patient with Hypercorticoadrenal Syndrome Contrasted with that Found in Addison's Disease. Endocrinology *21: 762*, 1937.

Wilson, D. M., Power, M. H., and Kepler, E. J.: Alkalosis and Low Plasma Potassium in a Case of Cushing's Syndrome: A Metabolic Study. J. Clinical Investigation *19:* 701, 1940.

Albright, F., Parson, W., and Bloomberg, E.: Cushing's Syndrome Interpreted as Hyperadrenocorticism Leading to Hypergluconeogenesis: Results of Treatment with Testosterone Propionate. J. Clin. Investigation *1:* 375, 1941.

Diseases of Gastro-intestinal Tract

Cave, Henry W., and Thompson, James E.: Mortality Factors in the Surgical Treatment of Ulcerative Colitis. Annals of Surgery *114:* 46 (July) 1941.

Livingston, Edward M., and Pack, George T.: End Results in Treatment of Gastric Cancer.

Allen, Arthur W., and Welch, Claude E.: Gastric Ulcer: The Significance of This Diagnosis and Its Relationship to Cancer. Annals of Surgery *114:* 498–509 (October) 1941.

Parsons, Langdon, and Welch: The Curability of Carcinoma of the Stomach. Surgery *6:* 327–338, 1939.

Gray, H. K.: Carcinoma of Stomach: Encouraging Results of Surgical Treatment. Proceedings of Interstate Postgraduate Medical Assembly of North America (1940), 139–141, 1941.

Gray, H. K., Walters, Waltman, and Priestley, J. T.: Report of Surgery of the Stomach and Duodenum for 1940. Proceedings of the Staff Meetings of the Mayo Clinic *16:* 721–736 (November 12) 1941.

Fansler, W. A.: The Origin of Polypi of the Large Bowel; with Especial Reference to Adenoma: Preliminary Report. J. A. M. A. *95:* 1969–1970, 1930.

Kennedy, R. L. J., and Weber, H. M.: Polyposis of the Colon in Children. Am. J. Dis. Child. *42:* 69–76, 1931.

Schmieden, V., and Westhues, H.: Zur Klinik und Pathologic der Dickdarmpolypen und deren Klinischen und Pathologischanatomischen Beziehungen zum Dickdarmkarzinom. Deutsche Ztschr. f. Chir. *202:* 1–124, 1927.

Wesson, H. R., and Bargen, J. A.: Classification of Polyps of the Large Intestine. Proc. Staff Meet. Mayo Clinic *9:* 789–794, 1934.

Bargen, J. Arnold: Important Newer Concepts Concerning Cancer of the Intestines and Their Bearing on Management. West Va. Med. Jr. *37:* No. 10 (October) 1941.

Thewlis, M.: The Care of the Aged (geriatrics). Mosby (St. Louis). 1941.

Boas, Ernest P.: Treatment of the Patient Past Fifty. Year Book Publ. Chicago. 1941.

McLester, J. S.: Borderline States of Nutritive Failure. J. A. M. A. *112:* 2110–2114 (May 27) 1939.

Schindler, R.: Early Diagnosis of Cancer of Stomach. Reprint 1939 from Journal National Cancer Institute *1:* No. 4, p. 451 (February) 1941. Also in J. A. M. A. *115:* 1693 (November 16) 1940.

Carey, J. B.: Gastroscopic Observation of Postoperative Stomach. Surg., Gynec. and Obst. *65:* 447 (October) 1937.

Moersch, H. J., and Walters, Waltman: Gastroscopic Observation of Postoperative Stomach. Surg., Gynec. and Obst. *71:* 129 (August) 1940.

Carey, J. B.: Gastroscopic Observation in Chronic Gastritis. Am. J. Dig. Dis. *7:* 160 (April) 1940.

Carey, J. B.: Observations in Achlorhydria. Am. J. Dig. Dis. (November) 1941.

Schloss, J., Ettinger, A., and Pratt, J.: Diagnosis of Diseases of Stomach by Gastroscopic and X-ray Relief Studies. Am. J. Med. Sc. *193:* 171 (February) 1937.

Templeton, R. E., and Schindler, R.: Diagnosis of Diseases of Stomach by Gastroscopic and X-ray Relief Studies. Am. J. Roent. and Rad. Therap. *41:* 354 (March) 1939.

Eusterman, G. B.: Peptic Ulcer: Medical Management. Minnesota Medicine *20:* 765–769 (December) 1937.

Eusterman-Balfour Text: The Stomach and Duodenum. Medical Treatment of Duodenal Ulcer. Chapter 13, pp. 275–294. Medical Treatment of Gastric Ulcer. Chapter 28, pp. 457–462.

Eusterman, G. B.: Carcinomatous Gastric Ulcer; Misleading Results of Medical Therapy. J. A. M. A. *118:* 1 (January 3) 1942.

Cardiovascular System

Clawson, B. J.: Rheumatic Heart Disease. American Heart Journal *20:* 454, 1940.

Clawson, B. J.: Incidence of Types of Heart Disease Among 30,265 Autopsies with Special Reference to Age and Sex. American Heart Journal *22:* 607, 1941.

Clawson, B. J.: Syphilitic Heart Disease. Syphilitic and Cutaneous Review *45:* 4, 1941.

Brown, James W.: Congenital Heart Disease. John Bale Medical Publications Ltd., 1939.

Abbott, M. E.: Atlas of Congenital Heart Disease. 1936.

White, P. D.: Congenital Heart Disease. Heart Disease.

Peters, H. C., and Visscher, M.B.: The Energy Metabolism of the Heart in Failure and the Influence of Drugs upon It. American Heart Journal *11:* 273, 1936.

Visscher, M. B.: The Energy Transformation by the Heart and the Mechanism of Experimental Cardiac Failure. Pub. No. 13, American Association for the Advancement of Science, pp. 176–183.

Harrison, Tinsley: The Failure of the Circulation. Williams and Wilkins. Baltimore.

Loeb, Robert F.: Plasma Proteins in Health and Disease. Reprinted from New England Journal of Medicine *224:* 980–987, 1941.

Page, Irvine H.: Newer Aspects of Experimental Hypertension. Reprinted from Publication No. 13 of American Association for the Advancement of Science, pp. 239–265.

Samuels, Saul S.: The Diagnosis and Treatment of Diseases of the Peripheral Arteries. Oxford University Press. New York. 1936.

Brown, George E., Allen, E. V. and Mahorner, Howard: Thrombo-angiitis Obliterans. W. B. Saunders Co. Philadelphia. 1928.

Collens, William S., and Wilensky, Nathan D.: Peripheral Vascular Diseases. Charles C. Thomas. Springfield, Illinois. 1939.

Infectious Diseases

Spink, W. W.: The Pathogenesis and Treatment of Staphylococcal Infections. The New International Clinics *4:* 236 (December) 1941.

Spink, W. W., Hansen, A. E., and Paine, J. R.: Staphylococcic Bacteremia: Treatment with Sulfapyridine and Sulfathiazole. Arch. Int. Med. *67:* 25, 1941.

Hoyt, W. A., Davis, A. E., and Van Buren, G.: Acute Hematogenous Staphylococcic Osteomyelitis. J. A. M. A. *117:* 2043 (December 13) 1941.

Kiefer, C. S.: Streptococcal Diseases. New Eng. Jr. Med. *220:* 109 (January 19) 1939.

Kiefer, C. S., Ingelfinger, F. J., and Spink, W. W.: Significance of Hemolytic Streptococcic Bacteremia. Arch. Int. Med. *60:* 1084 (December) 1937.

Bliss, E. A., Long, P. H., and Feinstone, W. H.: The Differentiation of Streptococci and Its Relation to Sulfanilamide Therapy. South. Med. Jr. *31:* 303 (March) 1938.

Reimann, H. A., and Havens, W. P.: An Epidemic Disease of the Respiratory Tract. Arch. Int. Med. *65:* 138 (January) 1940.

Ellis, R. V., and McKinlay, C. A.: Allergic Pneumonia. Jr. Lab. and Clinical Medicine *26:* 1427 (June) 1941.

Spink, W. W.: Sulfonamide Therapy. Year Book Publishers, Inc., Chicago. 1941.

Hitchens, A. P., and Campbell, E. P.: Communicable Diseases and Military Medicine. Medical Clinics of North America *25:* 1589 (November) 1941.

Top, F. H.: Handbook of Communicable Diseases. The C. V. Mosby Company, St. Louis. 1941.

Cecil, Russell L.: The Control of Respiratory Infections. Preventive Medicine, New York Academy of Medicine *9:* p. 64 (June) 1939.

Dochez, H. R., Mills, Katherine C., and Kneeland, Yale, Jr.: Filterable Viruses in Infections of the Upper Respiratory Tract. J. A. M. A. *110:* p. 127 (January 15) 1938.

Diehl, H. S., Baker, A. B., and Cowan, D. W.: Cold Vaccines. An Examination Based on a Controlled Study. J. A. M. A. *111:* p. 1168 (September 24) 1938.

Sherman, J. B.: Prophylaxis of the Common Cold. British Medical Journal *2:* p. 903 (October 29) 1938.

Diehl, H. S.: Medicinal Treatment of the Common Cold. J. A. M. A. *101:* p. 2042 (December 23) 1933.

Spink, W. W., and Hoffbauer, F. W.: Brucellosis (Undulant Fever): A Brief Review with Case Analysis. Reprinted from The Journal-Lancet LXI: No. 1, 13 (January) 1941.

Simpson, Walter M.: The Diagnosis and Management of Brucellosis. Reprinted from Ann. Int. Med. *15:* No. 3 (September) 1941.

TUBERCULOSIS

COURSE No. 11

Monographs

Alexander, John. The Collapse Therapy of Pulmonary Tuberculosis. Thomas, Springfield, Illinois. 1937.
Chapter by Max Pinner on "Physiological Principles of Collapse Therapy and Pathology of Pulmonary Collapse."
Chapters by John B. Barnwell on "Pneumothorax."
Tuberculosis and Leprosy. Symposium Series. Amer. Assoc. Adv. Science, 1938.
Terplan, K. Anatomical Studies on Human Tuberculosis. Suppl. Amer. Rev. Tuberc. *42:* 1 (Aug.) 1940.
Lurie, M. B. Heredity, Constitution and Tuberculosis. Suppl. Amer. Rev. Tuberc. *44:* 1 (Sept.) 1941.
Sweany, H. C. Age Morphology of Primary Tubercles. Published by C. C. Thomas, Springfield, Illinois. 1941.

Tuberculosis of Trachea and Bronchi

Barnwell, J. B., et al. Ulcerative Tuberculous Tracheobronchitis. Amer. Rev. Tuberc. *36:* 8 (July) 1937.
Bugher, J. C., et al. Tuberculous Tracheobronchitis: Its Pathogenesis. Amer. J. Med. Sc. *193:* 515 (April) 1937.
Ornstein, G. G., and Epstein, I. G. Tuberculosis of the Major Bronchi, etc. Quart. Bull. Sea View Hosp. *3:* 109 (Jan.) 1938.
Riggins, H. McL. Tracheobronchial Tuberculosis, etc. Trans. 35th Annual Meeting Nat. Tuberc. Assoc., 1939.
Myerson, M. C. Tuberculosis of the Trachea and Bronchi. J. A. M. A. *116:* 1611 (April 12) 1941.

Pleuropulmonary Fistula

Matsuzawa, D. The Behaviour of Pneumothorax Gases in the Early Period of Artificial Pneumothorax. Quart. Bull. Sea View Hosp. *2:* 363, 1937.
Matsuzawa, D. The Diagnosis of Pleuro-Pulmonary Fistula by Pneumothorax Air Analysis. Quart. Bull. Sea View Hosp. *4:* 286 (April) 1939.
Coryllos, P., and Welkind, A. The Diagnosis of "Silent" Broncho-Pleural Fistula by Pleural Gas Analysis. Quart. Bull. Sea View Hosp. *4:* 377 (July) 1939.
Matsuzawa, D. The Effect of Pneumothorax Pleuritis and Effusions Upon the Behavior of Pneumothorax Cases. Quart. Bull. Sea View Hosp. *5:* 40 (Oct.) 1939.
Matsuzawa, D. A Gas Sampling Tube with a Manometric Attachment for the Study of Pneumothorax Gases. Quart. Bull. Sea View Hosp. *5:* 186 (Jan.) 1940.
Matsuzawa, D. Diagnosis of Broncho-Pleural Fistula in Tuberculous Empyema. Quart. Bull. Sea View Hosp. *6:* 50 (Oct.) 1940.
Welkind, A. and Herman, M. Rapid Re-Expansion of Lungs; Pleural Lavage with Oxygen. Quart. Bull. Sea View Hosp. *4:* 153 (Jan.) 1939.

Gastric Lavage, Monaldi Suction, Pneumo-peritoneum, etc.

Kayne, G. G., Pagel, W., and O'Shaughnessy, M. Pulmonary Tuberculosis. Oxford University Press, 1939.
Chapters on Allergy, Immunity and Pathogenesis.
Miller, J. A., and Wallgren, A. Pulmonary Tuberculosis in Adults and Children. N. Y. Nelson. 1939.
Rich, A. R., and McCordock, H. A. An Inquiry Concerning the Rôle of Allergy, Immunity and Other Factors of Importance in the Pathogenesis of Human Tuberculosis. Bull. J. H. Hosp. *44:* 273, 1929.

Miller, J. A. Haematogenous Pulmonary Tuberculosis. Amer. Rev. Tuberc. *29:* 489, 1934.

Roper, W. H., and Ordway, W. H. Gastric Lavage in Adults with Pulmonary Tuberculosis. Amer. Rev. Tuberc. *43:* 543, 1941.

Mishulow, L., Kereszturi, C., and Hauptman. The Demonstration of Tubercle Bacilli in the Sputum, Faeces and Stomach Contents of Tuberculous Children. Amer. Rev. Tuberc. *29:* 471, 1934.

Banyai, Andrew L. Therapeutic Pneumo-peritoneum. Amer. Rev. Tuberc. *29:* 603, 1934.

Salkin, David. Pneumo-peritoneum in Intestinal Tuberculosis. Amer. Rev. Tuberc. *33:* 435, 1936.

Brown, L., and Sampson, H. L. Intestinal Tuberculosis. Lea and Febiger. 1930.

Trimble, H. G., and Wardrip, B. H. Pneumo-peritoneum in Treatment of Pulmonary Tuberculosis. Amer. Rev. Tuberc. *36:* 111, 1937.

Goldman, A., Brunn, H., and Ackerman, L. Tuberculous Cavities. Observations on Trans-pleural Decompression. Amer. Rev. Tuberc. *43:* 151, 1931.

Guggenheim, A., and Finkelstein, M. Continuous Transthoracic Aspiration of Pulmonary Cavities. Rky. Mt. Med J. *38:* 45, 1941.

Eloesser, L. Blocked Cavities in Pulmonary Tuberculosis. J. Thor. Surg. *7:* 1, 1937.

Kupka, E., and Wells, R. Technique of Cavity Aspiration (Monaldi), Amer. Rev. Tuberc. *42:* 401, 1940.

Kupka, E., and Bennett, E. S. Monaldi's Suction Aspiration of Tuberculous Cavities. Amer. Rev. Tuberc. *42:* 614, 1940.

Silicosis Bibliography

First, Second, Third and Fourth Saranac Laboratory Symposia on Silicosis. Edited by B. E. Kuechle, Wausaw, Wisconsin. 1934, 1935, 1937 and 1939.

Tuberculosis in Industry, 1940. The National Tuberculosis Association, 1790 Broadway, New York City.

National Silicosis Conference, Bulletin No. 21. Parts 1, 2, 3, and 4. 1938. U. S. Dept. of Labor, Washington, D. C.

Teleky, R. Pneumoconiosis. 1938. Supplements to the encyclopaedia entitled, "Occupation and Health." The International Labour Office, 734 Jackson Place, Washington, D. C.

Middleton, E. L. Silicosis. 1938. Supplements to the encyclopaedia entitled "Occupation and Health." The International Labour Office, 734 Jackson Place, Washington, D. C.

Amor, A. J. X-ray Atlas of Silicosis. Williams and Wilkins Co., Baltimore, Md., 1941.

Journals

American Review of Tuberculosis.
Quarterly Bulletin of the Sea View Hospital.

Excellent reviews on tuberculosis and other acute chronic pulmonary disorders may be found in review articles in the following journals:

American Journal of Medical Science.
Archives of Internal Medicine.
New England Journal of Medicine.

Announcements

Charles H. Swift, chairman of the board of directors of Swift & Company, has announced the establishment of a series of fellowships for research in nutrition. The

fellowships are intended to aid the federal government in its long-range national nutrition program.

The fellowships provide for special research to be undertaken in laboratories of universities and medical schools with funds which the company has set aside as grants in aid, beginning November 1, 1941. The fellowships will be for one year but may be renewed where the project warrants it. Any fundamental study of the nutritive properties of foods or the application of such information to improvement of the American diet and health will be eligible for consideration for a grant.

The Medical and Surgical Relief Committee of America, 420 Lexington Avenue, New York, N. Y., has as its objective to make up, through the coöperation of a nationwide committee of some 350 prominent physicians and surgeons, shortages in surgical and medical supplies in America. On December 15, 1941, at the request of Mayor Angelo J. Rossi, of San Francisco, two complete medical catastrophe units were shipped to the West Coast—the shipment being made in keeping with the Committee's new policy of concentrating future activities on furnishing aid to American hospitals and other organizations where they are required for emergency use. Arrangements are now under way to send similar first-aid medical and surgical units to hospitals in the States of New York, South Carolina, Maine and Vermont in response to urgent requests.

The next annual meeting of the Mississippi Valley Medical Society will be held September 30 to October 2, 1942, at Quincy, Ill.

The 71st Annual Meeting of the American Public Health Association will be held in St. Louis, Mo., October 26–30, 1942.

The biennial meeting of the Rocky Mountain Medical Conference will be held in Albuquerque, N. M., May 18–20, 1943.

The Dallas Southern Clinical Society will hold its 14th Annual Spring Clinical Conference March 23–26, 1942. Among the honor guests at this meeting will be: Dr. Edward G. Billings, F.A.C.P., Associate Professor of Psychiatry, University of Colorado School of Medicine, and Director of Psychiatric Liaison Department, Colorado General and Colorado Psychiatric Hospitals, Denver; Dr. Lewis M. Hurxthal, F.A.C.P., Physician-in-Charge, Department of Internal Medicine, Lahey Clinic, Boston, Mass.; and Dr. Andrew C. Ivy, F.A.C.P., Nathan Smith Davis Professor of Physiology and Pharmacology, Northwestern University Medical School, Chicago, Ill.

Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., who is Secretary of the Mississippi Valley Medical Society, has announced that the Society offers annually a cash prize of $100.00, a gold medal, and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics) and practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association who are residents of the United States. The winner will be invited to present his contribution before the next annual meeting of the Mississippi Valley Medical Society at Quincy, Ill., September 30–October 2, 1942, the Society reserving the exclusive right to first publish the essay in its official publication, the *Mississippi Valley Medical Journal*. Contributions shall not exceed 5000 words, be typewritten in English in manuscript form, submitted in five copies and be received not later than May 1, 1942.

OBITUARIES

CAPTAIN JESSE BUNDREN HELM

Captain Jesse Bundren Helm, Medical Corps, U. S. Navy, retired, died in the Garfield Hospital, Washington, D. C., November 26, 1941, of hypertensive heart disease, at the age of 56.

Captain Helm was born in Tennessee in 1885. He attended the Edwards Seminary at White Pine, Tenn., and received his medical degree in 1911 from the University of Louisville School of Medicine. He entered the Naval service July 20, 1913, and served in various positions until August 1, 1940, when he retired for disability incurred in the line of duty. He was a member of the Southern Medical Association and Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1936.

DR. JOHN ARTHUR ALVAREZ

Dr. John Arthur Alvarez was born August 13, 1905, at Fort Smith, Ark. His academic education was received at the University of Arkansas, at Fayetteville, from which he was graduated with the degree of B.A. in 1926. He graduated from Tulane University of Louisiana School of Medicine, New Orleans, in 1930, after which he served a two-year internship at the Charity Hospital in that city. He served as resident physician at St. Joseph's Infirmary in Houston, Tex., in 1932, and then spent two years in the Department of Medicine of the Harvard Medical School and the Peter Bent Brigham Hospital, Boston, Mass. Dr. Alvarez entered the practice of Internal Medicine in Houston, in 1934, and rapidly became one of the leaders in his chosen profession. He was a member of the Staff of the Medical Clinic of the Hermann Hospital, and an Associate in Medicine at St. Joseph's Infirmary in Houston. He was a member of the Harris County and Texas State Medical Societies, American Medical Association and American Heart Association. He was a Diplomate of the National Board of Medical Examiners and of the American Board of Internal Medicine, and since 1940 had been a Fellow of the American College of Physicians.

Dr. Alvarez died on October 19, 1941, as a result of a fibrosarcoma of the chest wall with lung metastasis, after an illness of several months. During these months Dr. Alvarez persisted in the pursuit of his usual duties and his fortitude and resignation were a support to his family and an object lesson to his colleagues. He is survived by his wife, his mother, and two sons.

The medical profession of Houston and all Texas has lost a most capable physician and a sincere friend.

M. D. Levy, M.D., F.A.C.P.,
Governor for Texas

DR. MARK TAD MORGAN

Dr. Mark Tad Morgan (Associate), Dayton, Ohio, died October 8, 1941, at Middletown, Ohio. He was born May 7, 1902, in Middletown, Ohio, and received both his pre-medical and medical training at Ohio State University College of Medicine, receiving his M.D. degree in 1929. He entered the Medical Corps of the U. S. Army and served at various stations in this country and in Hawaii until August 31, 1940, when he retired for physical disability. He had attained the rank of Captain.

From December, 1940, until the time of his death he was associated in practice with Dr. Warren C. Breidenbach, F.A.C.P., Dayton, Ohio. He was Junior Chest Consultant to the Miami Valley Hospital; a member of the staff (Diseases of the Chest), Good Samaritan Hospital; and Assistant to the Director, Stillwater Sanatorium.

From both a medical and personal standpoint Dr. Morgan was outstanding, and his death was a deep blow to those associated with him.

DR. IRA A. DARLING

Dr. Ira A. Darling died suddenly at 9:30 p.m., October 10, 1941, at the Torrance State Hospital, Torrance, Pa., where he had been superintendent since 1940. The immediate cause of death was coronary thrombosis.

Dr. Darling was born on March 9, 1888, at Aolcott, Vermont. He was left an orphan at an early age and moved to Meredith, New Hampshire, where he lived until he was ready to begin his pre-medical education, which was obtained at the Tilton Seminary, Tilton, New Hampshire. He entered the University of Vermont Medical School in 1907 and graduated in 1911. After a year's internship at the Lynn General Hospital he joined the medical staff at the Warren State Hospital, Warren, Pa., where he served as assistant physician and assistant superintendent under that outstanding neuropsychiatric administrator, Dr. Harry Mitchell.

Dr. Mitchell and Dr. Darling early recognized that the sound approach to neuropsychiatry was by means of a thorough physical as well as mental survey. Hence, they established at the Warren State Hospital a modern, well-equipped laboratory under the direction of a competent pathologist so that their patients could have the benefit of thorough scientific study. They also recognized the value of physical and occupational therapy and recreation in the restoration of their patients to as near a normal state of health as possible.

When Dr. Mitchell died in 1933, it was but natural that the board of directors should appoint Dr. Darling as superintendent. He continued as a most efficient administrator of the hospital until 1936 when a change in the state administration supplanted the boards of directors and superintendents with its own appointees for political and patronage reasons. It will indeed

be a fortunate day when the administrators of our state and municipal institutions of health are career men instead of political appointees.

Dr. Darling with his administrative experience, professional attainments and character easily won through civil service competitive examinations the appointment of superintendent of the Springfield State Hospital of Sykesville, Maryland, where he served with ability and distinction until 1940.

In the meantime, there had been another change of administration in Pennsylvania, and he was called back to be superintendent of the Torrance State Hospital during a period of reconstruction and reorganization. While he was at Torrance less than two years, his associates there acclaim his ability as an organizer and administrator.

Dr. Darling was always a loyal and public spirited citizen. During the first world war, he was commissioned a First Lieutenant in the Medical Reserve Corps on December 28, 1917. He served with the American Expeditionary Force in France, partly with Base Hospital 89 and partly with the 138th Field Artillery. He was discharged from service in January, 1919, and resumed his duties at the Warren State Hospital. In the present emergency he was appointed by the Governor as consultant in neuropsychiatry for Pennsylvania Local Draft Board, Area No. 8.

At the time of his death, Dr. Darling was a member of his county and state medical societies, of the Pittsburgh Neuropsychiatric Society, a Fellow of the American Medical Association, a Fellow of the American Psychiatric Association, a Fellow of the American College of Physicians, a Diplomat of the American Board of Psychiatry and Neurology, and a member of the Executive Committee of the Mental Hygiene Division Public Charities Association of Pennsylvania.

Dr. Darling is survived by his wife, Mrs. Jennie McGill Darling, and his daughter, Miss Ella Darling, both residing at Williamsport, Pa.

FREDERICK B. UTLEY, M.D., F.A.C.P.,
Pittsburgh, Pa.

LIEUT.-COL. GERALD ROSS BURNS

Dr. Gerald Ross Burns died on November 16, 1941, a few days after he had undergone an emergency operation. He became ill while on duty at Debert, N. S., where he was serving with His Majesty's Army as officer in charge of medicine, No. 7 Canadian General Hospital.

Though only about 40 years of age, Dr. Burns held an enviable record in the field of medicine. He also took an active part in community affairs and other varied interests, and there are many institutions in Halifax that will mourn the passing of a true benefactor who gave much of his time, skill, and substance to charitable works.

Surviving Dr. Burns are his wife and two small children; his mother, two brothers, Right Rev. W. J. Burns and Rev. Dr. John E. Burns; and two sisters, Miss Eileen and Miss Eveleen.

Dr. Burns received his B.A. degree from St. Marys College, Halifax, and his medical degrees from Dalhousie University. Following graduation, he was Assistant Superintendent of the Nova Scotia Sanatorium and later took a postgraduate course at the University of Pennsylvania. For the past ten years he acquitted himself honorably and well as a specialist in internal medicine, as Assistant Professor of Medicine at Dalhousie, and in many other important medical posts at Halifax, N. S. He entered upon his army duties at the outbreak of war and gave all his time and energy to war work, in which his achievements were notable; and only his untimely death prevented him from serving his country overseas. He had been a fellow of the American College of Physicians since 1938.

Patriot, physician and teacher he was buried on November 16, surrounded as a Christian medical officer should be by members of the clergy, army, medical profession, medical students, former patients and friends; and with the last impressive rites of his church and the full military honors of the army of His Majesty the King, in whose uniform he answered the call to higher and fuller service.

J. W. MacIntosh, M.D., F.A.C.P.,
Halifax, N. S.

COLONEL M. A. DAILEY

Dr. Michael Andrew Dailey, Colonel, Medical Corps, U. S. Army, Surgeon Third Corps Area at Baltimore was fatally injured on October 27, 1941, when the automobile in which he was returning to Baltimore from Fort Meade, Maryland, was struck by an express train at Jessup station. Lieut. Colonel Howard E. Ashbury of the Army Medical Reserve, formerly Surgeon of the 4th Infantry Md. N. G., who was riding with Colonel Dailey was seriously injured.

Colonel Dailey was born on October 31, 1882, in North Easton, Mass. He was graduated from Dartmouth College in 1904 and from the Harvard Medical School in 1907, following which he served an internship in the Boston City Hospital. He was commissioned in the medical reserve corps of the Army in September 1911 and sent to the Army Medical School in Washington. Following graduation here he was commissioned in the regular corps on May 12, 1912, and ordered to Fort Sheridan, Illinois. Following a tour on the Mexican border at Fort Bliss, Texas (1913–14) he served two years in the Philippine Islands (1914–16). The World War found him in Fort Yellowstone, Wyoming, from which station he was ordered in August 1917 to New York City to take command of Base Hospital No. 3 which was being organized at the Mount Sinai Hospital. In February the unit sailed for Europe and in May was operating at Vauclaire in the Department of Dordogne. He commanded this unit until October 1918. Later he was on hospital duty at Rennes, Ill-et-Vilaine. Returning to the United States in November 1919, he served for four years in posts in Texas and then was

transferred in December 1923 to the post of assistant to the Surgeon, Sixth Corps Area in Chicago. Always a keen student of internal medicine, he was detailed in December 1927 to Beaumont General Hospital as head of the medical service. In 1932 he was transferred to a similar position in the Walter Reed Hospital in Washington. A recent duty was the command of Gorgas Hospital at Ancon in the Canal Zone, from which service he returned in August 1941, taking over the place in the Corps Area Headquarters at Baltimore.

Colonel Dailey was one of the Army's notable specialists in internal medicine. His preparation for this work included a course at the Mayo Clinic. He was a fellow of the American College of Physicians and a diplomat of the American Board of Internal Medicine.

Colonel Dailey was married to Joeen Margaret O'Brien, who with two sons and a daughter, survives him.

A large funeral cortege accompanied the remains from Baltimore to the Memorial Chapel at the Army Medical Center on October 30, where services were conducted by Chaplain Edward J. McTague of Walter Reed Hospital. Interment was in Arlington National Cemetery.

HISTORY OF PIONEER MEDICAL PRACTICE IN ST. PAUL *

By J. M. Armstrong

In the year 1847, Dr. John Jay Dewey established himself at Saint Paul's Landing, now known as Saint Paul. Dr. Dewey was a younger brother of the Governor of Wisconsin Territory and as Wisconsin was about to become a state, it was surmised that a new territory would be set up to the west, and that the capitol of the new territory would be a desirable place to settle. This we believe was the reason that influenced Dewey to come here.

At that time our population numbered about forty. Dr. Dewey was a man of 25, had graduated from the Albany Medical College in March of that year, and remained here until his death in 1891.

When Minnesota Territory was established in 1849 with Saint Paul as its capitol, the town took on a rapid growth, there being about 300 inhabitants by the end of the year, and the number of physicians increased to six. Dr. Thomas R. Potts became the first president of the Trustees of the town, and Dr. David Day, Register of Deeds. Both these men were graduates of the University of Pennsylvania and both resided here the rest of their lives.

From this time on the town increased rapidly in population and not a few medical men made a trial of the practice of their professions here. Many of them remained but a short time, moving to other parts of the territory as settlement progressed.

In 1853 the first medical society in the territory was organized in Saint Paul, called "The Minnesota Medical Society." At that time there were about 20 medical men in the territory, and 13 of them responded to the call of the organizers. This society lived until 1857, when the last annual meeting was held in St. Ansbury, now part of Minneapolis. The financial panic of that year undoubtedly was the cause of its demise.

In 1850, Saint Paul had a population of 10,279, so one can see that growth was considerable. However, fur trading, the exportation of pine lumber and cranberries were the only industries.

In the year 1853, the cornerstone of our first hospital, and the first in the territory, was laid, but it did not open for patients until 1855. In 1854 and 1855 our city was invaded by an epidemic of Asiatic cholera which took its toll of both immigrants and residents, and put a severe test on the town.

In 1857 the predecessor of St. Luke's Hospital was established. It was not until many years later that other hospitals which now number 16 were established. At present these hospitals can care for 2,863 patients, and have 261 bassinets.

* The American College of Physicians will hold its Twenty-Sixth Annual Session in St. Paul, April 20–24, 1942.

In 1860 the Saint Paul Academy of Medicine and Surgery, our first local medical society, was formed. It was a most successful organization. A medical library was established, a laboratory put in operation, and a microscope and an electrical machine purchased. Some instruction to medical students was also given by its members in its halls. Unfortunately for this society, the Civil War interfered with its functions as all its members went into the army. When the war was over many new practitioners had settled in Saint Paul, and it was thought that since the members of the Academy could not take in the newcomers without sacrificing their funds, and since all had to recoup their fortunes, it would be wisest to disband. The lot that had been purchased for a home was sold, the books in the library returned to the donors, and the laboratory apparatus disposed of.

Informal medical meetings were held here until our Ramsey County Medical Society was organized in 1870, a year later than our present State Association. Since then our Society has had a prosperous career and many local and special medical societies have been organized.

Medical journalism and medical teaching started in Minnesota this same year, 1870, with the establishment of the Northwestern Medical and Surgical Journals, and the opening of the Saint Paul Medical College in Saint Paul by Dr. Alexander J. Stone. The journal, a quarterly, lasted four years and the Medical School until 1888 when the medical department of the University of Minnesota was established in Minneapolis with practically the entire teaching staff of the Saint Paul School on the faculty.

Since 1870 Saint Paul has been well known as a medical center, and many eminent physicians have practiced their profession here. The Medical Journal now known as the Journal-Lancet, was established in Saint Paul by Dr. Stone in 1881, but is now published in Minneapolis.

In 1899 the Saint Paul Medical Journal was started by the Ramsey County Medical Society and continued until 1917 when "Minnesota Medicine," the organ of the State Medical Association, was established, the Saint Paul Journal agreeing to disband its publication to protect the new journal.

The Ramsey County Medical Society has, since 1899, a well equipped and maintained medical library, adequately housed and supported, with a trained medical librarian in charge and containing 25,000 books and bound journals. The funds to support this library are derived from interest on a fund accumulated from the sale and manufacture of surgical ligatures, which enterprise was started by Dr. Edward Boeckmann over 40 years ago, and also from profits from the now defunct Saint Paul Medical Journal.

The medical practitioners of Saint Paul are proud of their past history and optimistic that their professional standing for the future is assured.